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Nasal Sinusitis[1]

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In previous articles, I have described the technic for x-ray examination of the sinuses which I believe desirable and necessary for dependable diagnosis. I will not repeat that discussion here further than to say that films of the highest grade of technical excellence are necessary, and that views must be taken in all positions that might give any additional information. Under the most favorable circumstances, there are enough inherent potential sources of error in sinus diagnosis without adding the unnecessary ones of poor technic.

Having obtained satisfactory films, it is still necessary to have some knowledge of the clinical aspects of the case if gross errors of interpretation are to be avoided. For instance, an antrum filled with polypoid tissue may look exactly the same on the film as it would if filled with pus. The knowledge that polypi were present in the nose, however, or that pus was draining from the antrum, would put an entirely different aspect on the situation. If the radiologist who interprets the films does not have this information, then the rhinologist who performs the physical examination must correlate his findings with the x-ray report, with a full understanding of the fundamental limitations of the x-ray and without criticism of his colleague. In this field of diagnosis co-operation is probably more important than in any other.

For purposes of discussion, sinusitis may be classified as follows:

Acute
1. Catarrhal
   - Hay fever
   - Cold in the head
2. Suppurative
   - Cold in the head
   - Contagious diseases
   - Acute fulminating

Chronic
1. Suppurative
   - Recurring attacks
   - More or less constant draining
2. Hyperplastic
   - Allergic
   - Edema of membrane
   - Polypi
   - Cysts
   - Complicating suppuration

ACUTE SINUSITIS

Acute catarrhal sinusitis is probably not often recognized, because there is little occasion to examine the sinuses roentgenologically in such cases. I believe any extended investigation of hay fever patients by x-ray would reveal a high percentage of opaque sinuses, particularly the maxillary, due to swelling and edema of the mucous membrane continuous with that in the nose. The same thing applies to the acute stage of a cold in the head. Interest in this type of sinusitis is, how-

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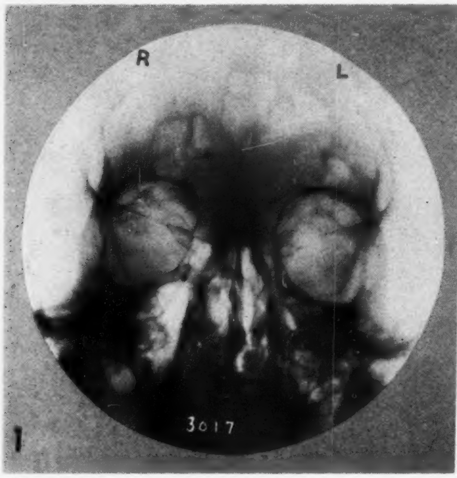


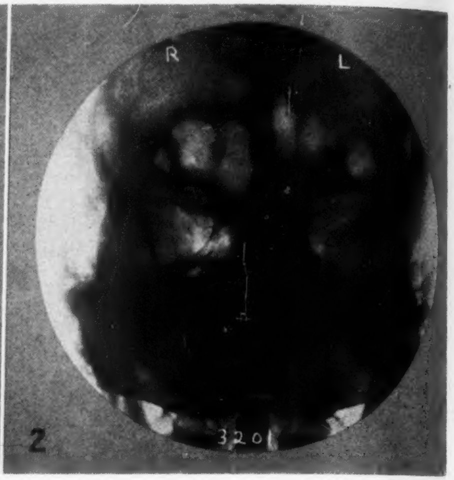


Fig. 1 (left). Acute fulminating catarrhal sinusitis. The sinuses were opened and no pus was found. Sinusitis was thought to be on an allergic basis in this case.

Fig. 2 (right). Acute suppurative sinusitis involving left frontal, left ethmoids, and both maxillaries. Fatal termination. Autopsy showed brain abscess without evidence of osteomyelitis of frontal bone.

ever, largely academic, as it has little clinical significance.

Acute suppurative sinusitis usually results either from the direct spread of infection from the nasal cavity in a head cold or as a complication of an infectious disease. Of these causes, influenza is undoubtedly the most common, but the acute contagious diseases of childhood are also frequent offenders.

The swelling of the nasal mucous membrane which accompanies these diseases blocks the drainage from the sinuses; the mucous secretion originating in these cavities cannot get out and quickly becomes infected by continuity with the infected membrane in the nose. The cavity most often infected in this manner is the maxillary, but ethmoid cells or frontal may also be involved.

Because drainage is usually completely obstructed, the involved cavity appears as a dense uniform opacity, the air space being completely filled with pus. After swelling of the nasal mucosa disappears, drainage is re-established, the sinuses are emptied of pus, and if roentgenograms are made at this time, the appearance may be entirely normal.

Acute fulminating sinusitis is a term applied to an acute sinusitis of such virulence that the infection spreads in a few days, not only to several cavities but usually also to surrounding soft tissues, to the orbits, to adjacent bone, and often to meninges or brain. The condition most often follows a common cold; the organism most frequently found is the staphylococcus, though occasionally streptococci or pneumococci are found. The gravity of this infection is revealed in the mortality rate, which is about 10 per cent. When death occurs, it is due to an overwhelming toxemia, to spread of the infection to intracranial structures, or to the development of osteomyelitis.

The x-ray diagnosis is complicated by the swelling and edema of the soft tissues of the face, which cause a generalized increase in density over all the sinuses and obscure the details of the sinus cavities. The involved sinuses are usually completely filled with pus and, consequently, cast uniformly dense shadows on the film. After the pus is evacuated, the edema of soft parts may cause a continued density and thus raise doubt as to whether all the pus has been drained.

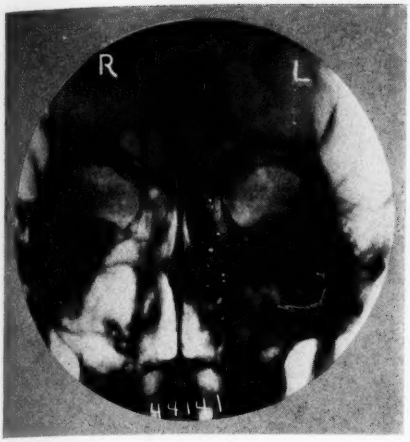


Fig. 3. Chronic suppurative sinusitis involving entire left side. Such cases usually show some hindrance to adequate drainage.

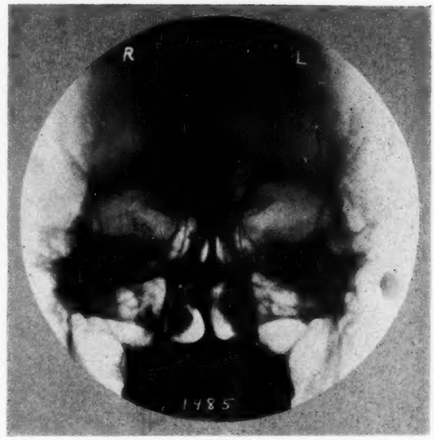


Fig. 4. Chronic suppurative sinusitis involving right frontal and right antrum. Film made in an interval when there was no pus production.

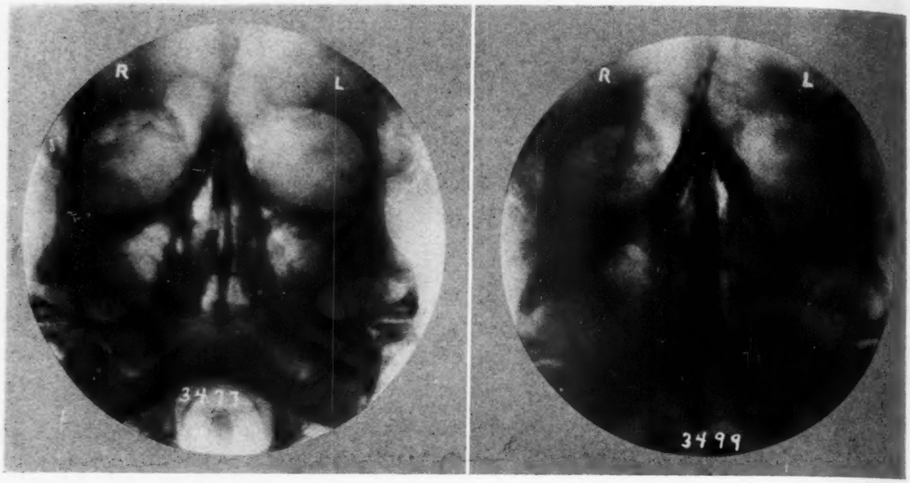
Involvement is usually multiple; seldom is the process confined to one cavity. Involvement of the ethmoids and frontals is often followed by extension into the orbit, the frontal bone, or the brain. Destruction of the walls of the orbit or osteomyelitis of the frontal bone is usually not difficult to recognize. Subperiosteal abscess on the exterior of the frontal bone, however, or subdural abscess on the inside, may develop without any of the usual signs of osteomyelitis. We have recently seen a case which at autopsy showed an abscess in each lobe of the cerebrum, without any recognizable sign of disease of the frontal bone either at autopsy or in the x-ray films. Probably the spread of infection in such a case is the result of a thrombophlebitis. McCollough (1) says that when a subperiosteal abscess is present, a subdural abscess will also be found.

Although the technical difficulties are increased in this type of case, the gravity of the situation demands the utmost care in attempting to detect involvement of bone surrounding the sinuses, particularly in the ethmoid region and frontal bone.

CHRONIC SINUSITIS

Chronic suppurative sinusitis practically always develops in a person whose nasal anatomy interferes in some degree with drainage from one or more of the sinus cavities. Such a person usually develops an acute sinusitis as a complication of some acute infection, and because of poor drainage the infection in the sinus continues for a protracted period. If the drainage is very bad, the infection is prolonged indefinitely and pus production in some amount goes on continuously. Occasionally various cavities will be filled with pus; sometimes they will be empty; usually there will be smaller amounts but not complete distention.

This type of case is more easily diagnosed than the other of which I shall speak presently, because inspection of the nose and nasopharynx will reveal the evidence of drainage. The exact status of affairs will not always be demonstrated by x-ray alone, since the character of the opacity may not be diagnostic. A sinus filled with pus has a more or less characteristic appearance, but an infected sinus which is producing pus and draining most of it may present an opacity practically identical with that seen where the mucous membrane is thickened from some previous attack now inactive. It is in this type of case that the detection of a fluid level in the sinus is important. Because of this,



Figs. 5 and 6. Chronic hyperplastic sinusitis with marked thickening of membrane in both maxillaries. Fig. 6 (right) was made with lipiodol in the left antrum. The marked thickening of membrane is nicely demonstrated by this procedure.

I believe sinus films should always be made with the patient sitting up, if possible. The demonstration of a fluid level is uncertain, however, even when the cavity is partly filled, for unless the beam of x-rays is directed parallel to the surface of the fluid, the shadow will be projected in such a manner as to make the cavity appear entirely opaque. A knowledge of the history and physical findings, together with the x-ray appearance, is necessary to make an accurate diagnosis in this type of sinusitis.

A second type of chronic suppurative sinusitis is that in which the patient has recurring acute attacks with quiet intervals between. For a time the sinuses may be essentially normal during these intervals, but after a number of attacks the lining membrane becomes thickened and fibrosed and eventually is probably never entirely free of infection.

In this type the drainage is better than in that just described and the sinuses are usually dry between attacks. Only during acute exacerbations the nasal membrane swells, the ostia become closed, and the cavities are filled with pus. At this time, the x-ray appearance is that of a pus-filled sinus. If, however, the patient is examined in an interval when no pus is present, the only finding will be a slight opacity produced by the thickened membrane.

The thickened membrane in these cases is quite different from that seen in hyperplastic sinusitis. In the latter, the membrane is greatly swollen and edematous; it may be as much as a centimeter thick. When seen on edge in the maxillaries, this very marked thickening is easily recognized. In suppurative sinusitis the membrane does not reach a thickness of more than one or two millimeters. It becomes fibrosed and adds a uniform increase in density, but it does not present a definite thick edge of the maxillary wall, such as is seen in the hyperplastic type.

Unfortunately for diagnostic purposes, the character of this opacity is the same whether it represents the result of one or more previous attacks of sinusitis now entirely healed, or whether the roentgenograms are made during an inactive interval of a chronic sinusitis. Small quantities of pus adhering to the membrane may look no different than a dry sinus. A sinus that has been operated on, with traumatism to the membrane, will always present a slight opacity afterward, which

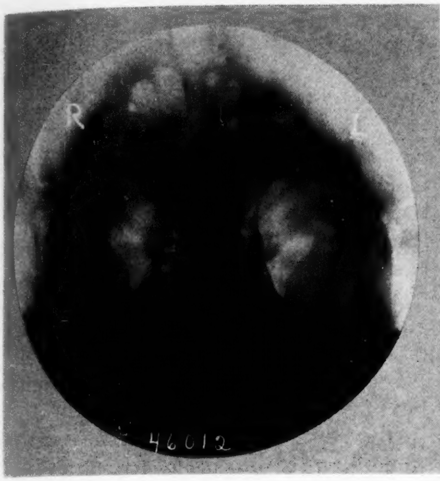


Fig. 7. Chronic hyperplastic sinusitis with diffuse polyposis in all of the sinuses. Note the marked widening in the ethmoid region, which the author believes is characteristic of polyps.

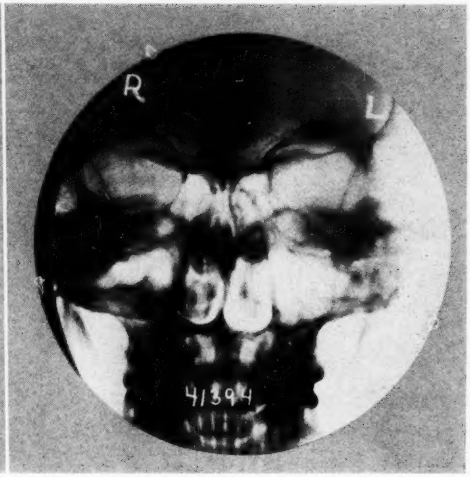


Fig. 8. Large cyst in the right maxillary sinus. This is manifested by a dense opacity in the inferior angle which has a smooth sharply circumscribed convex upper border.

looks quite the same as a dry sinus during a quiet interval in a chronic suppurative case.

Sinusitis is a frequent complication of influenza, and if it persists for a time after this infection, a thickened membrane may result which will produce a slight permanent opacity, without sinusitis and, of course, without pathological significance.

Because of these various confusing conditions, a history of the case is essential to accurate interpretation of the x-ray films, as well as a knowledge of the physical findings, particularly in respect to drainage.

Osteomyelitis, in our experience, has occurred much more often as a complication of acute than of chronic sinusitis. In chronic types, it may follow operation or, less frequently, occur spontaneously. It is recognized by bone necrosis adjacent to the frontal sinuses or in the ethmoid region. It is usually not difficult to recognize this complication, but its eradication is not so simple.

Chronic hyperplastic sinusitis is considered by most authors to be inflammatory in character and not an infectious process, although one occasionally reads about the infection in these cases.

Lee M. Hurd (2) suggests that all polypoid cases are probably allergic. The discharge from these cases, when present, is a clear, viscid, very irritating fluid, definitely not purulent. In some cases there is no discharge at all. A fact that may be overlooked is that in a case of hyperplastic sinusitis there may develop a superimposed purulent infection, with discharge of pus. In a case of this sort, one may recognize both suppurative and hyperplastic sinusitis.

The characteristic x-ray findings depend upon the marked edema and swelling of the mucous membrane. Because of the swelling, the ostia of many mucous glands become clogged and tiny mucous cysts add to the thickness of the membrane. The swollen membrane in places forms folds, and, according to Hirsch (3), the resulting prolapsed mucosa produces the polypi which accompany this condition. Larger retention cysts may also develop and are recognizable by their round, smooth outline. The very thick membrane can be seen only in the antrum, where it may reach a thickness of as much as a centimeter, and is easily recognizable around the walls of the cavity. In some

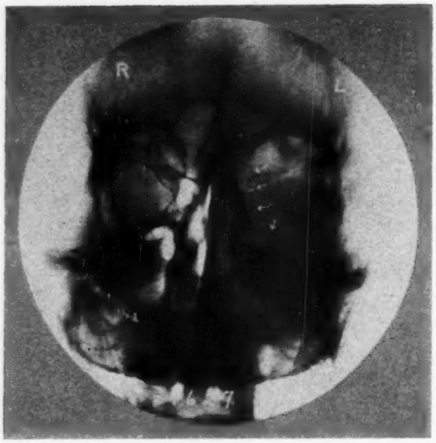


Fig. 9. Carcinoma which extended into left antrum from the left upper molar region and has caused extensive destruction of bone in the ethmoid region.

instances, numerous small polypi occupy practically the entire membrane and add to its thickness. Single polypi are recognizable only if they reach considerable size. The same applies to cysts, which are often seen. Camp has called attention to the fact that most of the large solitary cysts seen in the antrum are congenital serous cysts and of no pathological significance. However, cysts do accompany hyperplastic sinusitis. Where cysts are seen, it is probably wise to consider them innocent unless other signs of hyperplastic sinusitis are also present, such as thickened membrane and polypi in the nose.

There are three x-ray signs of polypi: (1) comparatively large, smooth, discrete shadows, round or pear-shaped; (2) a very thick membrane, due to polypoid degeneration; (3) a decided widening of the ethmoid regions recognizable in postero-anterior views, due to distention and bulging of the ethmoids from the many polypoid growths.

The diagnosis of hyperplastic sinusitis depends upon the recognition of thickened membrane, polypi, or cysts, and cannot be made otherwise by x-ray films. Recognition of these pathological changes is often facilitated by the injection of lipiodol into the antrum. The thickened membrane and the round defects produced by the polypi and cysts are brought out clearly by this method.

If the patient has a superimposed purulent infection, the hyperplastic changes cannot be recognized until the pus is drained. Sometimes, however, one may see an antrum on one side filled with pus, while the other shows the characteristic shadows of hyperplastic sinusitis. Multiple views are desirable, as the characteristic changes may be visualized in one plane but not in others. Where the sinus cavities are entirely filled with hyperplastic tissue, the appearance may be indistinguishable from those filled with pus. In such a case, examination of the nose will practically always reveal polypi, again emphasizing the value of a knowledge of clinical evidence in making a diagnosis.

Malignant neoplasms involving the accessory sinuses may be mistaken for sinusitis. As a matter of fact, many neoplastic growths become infected and an actual suppurative sinusitis is also present. Sarcoma involving the sinuses may arise in the nose or in the bone adjacent, usually the superior maxilla. Sarcoma in the nose eventually results in complete destruction of all the bony structures there, and the large vacant area resulting produces a very characteristic picture. Sarcoma of the bones of the face also produces destruction, and the diagnosis rests on these bone changes rather than any appearance of the sinuses.

Carcinoma may arise primarily in the antrum but to the best of my knowledge, I have not recognized such a case. The majority of such growths evidently arise either in the mucous membrane of the nostril or in the mouth, usually around a molar tooth. From this location the lesion invades the antrum or, if primary in the nostril, may spread to the ethmoids. In my experience, the usual extension is into the antrum first and from there to the ethmoids.

At this time, the only x-ray change noted may be an opaque antrum, due

probably to both cancer tissue and pus. When the disease extends beyond the antrum, the floor of the orbit is usually at least partly destroyed and, as invasion continues into the ethmoids, bone destruction there is usually also obvious. The x-ray diagnosis of a malignant growth involving the accessory sinuses is thus seen to depend upon changes in the surrounding bone rather than upon any characteristic appearance of the sinuses themselves.

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DISCUSSION

John D. Osmond, M.D. (Cleveland, Ohio): It is a pleasure to discuss Dr. Grier's paper for I have a high regard for his work.

We all agree that a correct diagnosis depends on excellent films made at various angles and different positions, together with a knowledge of the various diseases that may be represented by abnormal densities, variation in outline of a sinus or cell wall, and changes in the thickness of a sinus membrane. The interpretation will be aided if one has had special training in rhinology or will apply a critical analysis of the clinical facts represented in each case.

The clinical facts must be obtained from the physician referring the case or from the patient himself. The history will give information as to whether or not a nasal discharge is present. If a discharge is present, is it purulent? Have there been previous attacks of sinusitis? Has there been an operation—an antrotomy or a Caldwell-Luc? Are nasal polypi present?

The history will narrow the differential diagnosis of opacities even if there is a circumscribed area of density or a general opacity. A slight uniform density may represent a recent slight inflammatory change, a suppurative sinusitis with good natural discharge or a hyperplastic sinusitis.

In case there has been an operation, the expression used by Dr. Frederick Baetjer in diagnosing bone tumor seems to me to be applicable: "After the surgeon has been in, all bets are off." There is so much difference in appearance after operation.

Hay fever and allergy are first cousins to the post-operative sinus case in causing a cloud of doubt and should be cleared by the history, if possible.

I would like to ask Dr. Grier about his sphenoid sinus films. In what position are they taken?

George W. Grier, M.D. (*closing*): I feel that for visualizing the sphenoid sinus the superior inferior view is absolutely indispensable. That should be a routine part of the examination of the sinuses. It does not matter, particularly, whether it is made from above downward or from below upward. Personally, I make it from above downward, usually with a Bucky diaphragm. I tilt the apparatus at an angle of 23° and have the patient sit with his chin extended over the apparatus so that the point of the chin rests on the top of the Bucky; then with the centering rod on the tubestand which would outline the central ray, I tilt the tube so that the pointer comes through the area where the sphenoid sinus would be, which of course is about half way between the external auditory meatus and the external margin of the orbit; the shadow is cast just posterior to the angle of the jaw. Or the patient may be placed with a pillow under his shoulders, and his head thrown back as far as possible until the vertex rests on the table top, the exposure being made from below.

In our routine examination we include the Granger position. Once in a while it gives some additional information. You will remember that Dr. Granger insisted that the patient be lying down. His sign depended on the gravitation of pus which might be in the sphenoid up against the roof of the sphenoid. So the patient is put on his stomach and the head tilted 17° beyond the horizontal. The shadow of the sphenoid is thrown into the area just between the frontals, just above the bridge of the nose, and you see the Granger line, which is the roof of the sphenoid. If there is pus in the sphenoid, then that sharp line is not seen.

High-Voltage Roentgen Irradiation of Accessible Cancer of Skin and Mucous Membrane[1]

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In our past experience, low-voltage roentgen treatment of malignant lesions of the skin, mucous membrane, and underlying structures has been attended by a relatively high percentage of early and late recurrences. Many of these lesions can be extirpated successfully and completely by any destructive agent provided it acts widely and deeply enough so that there are no remaining viable malignant cells, and with a minimum of lethal effect on normal tissue. Roentgen treatment must be rationalized to produce the optimum effect in a field not only including the lesion but extending beyond it into the zone of normal tissue in depth as well as laterally. Too often we think of cancer as spreading peripherally, without taking into consideration the fact that the malignant cells tend to invade in all directions, including the deeper structures. The treatment of accessible lesions must be designed to destroy the deeper areas of invasion as well as those which can be observed on the surface.

We believe that some of our failures of the past have been due largely to the use of massive caustic dosage with x-rays of low voltage and little or no filtration, or to the employment of too small fields. It is true that the ideal procedure would be to vary the penetration by changes in voltage, filtration, and distance, according to the depth of extension of the tumor and its surrounding infiltration, but since there is no practical method of doing this, it is quite impossible to predict in advance the optimum penetration. It is better to give too great a depth dose than too little, in order to be certain of the death of all underlying, deep, viable cancer cells. For this reason, in many of our larger tumors of grades 2 and 3 (according to James Martin's clinical classification based on gross size and appearance) we have employed a voltage of 200 kv. (peak), with filtration of at least 0.5 mm. of copper plus aluminum.

The depth dose at 5 cm. is greater, in a field of equal size, with this voltage than with 80 to 130 kv., more or less commonly used in superficial therapy. The objection, however, may be offered that with high voltage there is danger of causing undesirable radiation changes in the very deep structures. We believe that we have at least partly obviated this danger, if it exists, by changing the direction of the beam at each treatment, while still confining the irradiation to the accessible involved area. Observing this precaution, we have seen no deleterious effects up to the present even when treating over the head and neck, or the more radiosensitive structures within the thoracic cage.

The reports of Murphy (8), Martin (6), Widmann (9, 10), Grier (11, 12), and others have shown good results with low-voltage, lightly filtered radiation and this technic must be given due consideration as an effective method of treatment. It may be that our failures with low voltage were due to the use of fields that were too small or to inadequate total dosage.

Our higher-voltage technic was evolved from observation of biological effects and clinical results not only in skin cancer but in the treatment of so-called plantar warts. In lesions of the latter type the generally accepted method of massive dosage and low voltage gave poor results in our hands, with a high percentage of failures and recurrences. The low-voltage rays proved to be destructive and irritating to the very superficial tissue but were not lethal to the deep areas of the verrucae, which, as we

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know, often have capillary loops extending 1 or even 2 cm. below the skin surface. The superficial destruction appeared, also, to inhibit the healing process, so that the lesions were often painful and disabling for a long period of time. As soon, however, as we began to give moderate doses, 200–400 r, with high voltage and heavier filtration, at intervals of one to three days, the verrucae disappeared promptly, usually after two to four treatments, and with no additional pain due to the irradiation. With certain changes this technic proved to be equally effective in the treatment of carcinoma of the skin and mucous membranes.

Our cases have been treated daily or on alternate days with 400 to 600 r measured on the skin, with an effective wave-length of 0.18 to 0.128 Ångström units (half-value layer 0.55 to 1.6 mm. copper), ten to fifteen treatments being given. The total dosage depends upon the skin reaction and response of the tumor. An effort is made to individualize each case and it is difficult to predetermine the exact dose which will be used. With the repeated fractional dosage method it is possible to gauge the amount of treatment by the resultant changes in the superficial tissues. This is of obvious advantage in the avoidance of over-treatment. Our experience has been that daily treatment is no more efficacious than treatment given on alternate days, and we are better able to evaluate our tissue reactions when using the longer interval.

According to Merritt and Rathbone (2), in the treatment of recurrent skin lesions, or epitheliomas involving bone or cartilage, with lightly filtered or unfiltered rays—the usual method—cancericidal doses tend to produce trophic ulcers with cancer cells still present in the base of the lesion. They state that in cases in which the treatment has been successful so far as the malignant growth is concerned, particularly if the lesion is extensive, "the remaining ulceration with its chronicity and attending pain has not infrequently been of such a nature as to nullify the good accomplished." They continue: "For several years we have used various technics in the roentgen ray treatment of extensive superficial malignant lesions, and because of the uniformly good results we believe that heavily filtered roentgen rays at voltage at or above 200 kv.p., represent a distinct advance in superficial cancer therapy." They are convinced, however, that 2 mm. of copper should be the minimum filtration for 200 kv. rays in treatment of malignant growth.

Dresser and Dumas (3) write: "It has been our experience that treatment of lesions 1 centimeter or more in thickness with long wave roentgen rays of little penetrating power or the beta rays of radium often results in primary healing, but with a high percentage of recurrences, presumably due to the fact that the base of the epithelioma has received too little radiation." They employ the usual 200 kv. (peak) setting with a filtration of 0.5 mm. of copper.

Wigby and Cohen (4), in a survey of the various technics employed in radiation therapy of carcinoma of the skin, found that there is a greater difference between the lethal dose for tumor tissue and for surrounding normal tissue with short wave-length therapy. They believe that "heavily filtered high-voltage x-rays provide more uniform distribution of radiation and a greater depth dose, factors which are indeed necessary to the destruction of the larger and more deep-seated lesions."

We have found that it is not advisable to rely on histological findings in the calculation of our total dosage. It is better to calculate the amount per treatment and the total dose according to the size and apparent extent of the tumor and its rate of regression during the period of irradiation. In certain cases the microscopic picture leads us to believe that we are dealing with a radiosensitive lesion and the clinical response proves to be incompatible with the biopsy findings.

In some instances large, thick, bulky tumors may be removed advantageously by electrodesiccation as deeply as the level of the skin surface. This operation can then

Figs. 1 and 2. Case 1: Extensive undermined area near the inner canthus of the right eye (Fig. 1, above). This had been treated elsewhere, within the past year, by mild doses of x-rays and surgical excision, followed promptly by recurrence. Three months after high-voltage therapy there was no evidence of recurrence and no appreciable scar; the skin was intact (Fig. 2, below).

be followed immediately by roentgen therapy, in conformity with the usual procedure. One must expect slower healing, with more scarring and telangiectasis.

Screening the normal tissue to within 0.25 to 0.5 cm. from the periphery of a carcinoma permits the normal skin to cover the treated area by epithelialization from the edges after the malignant cells are destroyed by the radiation. This usually occurs in less than six weeks, provided the optimum dosage is given. We believe that it is unwise to treat a field larger than 5 cm. in diameter with this technic, as the advantages may be outweighed by retardation of the reparative process, due to edema of the subcutaneous tissue in an area that is too wide.

On account of the less irritating effects of radiation of shorter wavelength, the new epithelium shows no early or late radiation damage. The new skin usually becomes normal in appearance, it is apparently well nourished, and no telangiectasis follows. This result is often impossible of attainment when low-voltage rays are used.

The problem in treating mucous membranes is not so difficult, because the recovery rate is much more rapid and it is not so important to screen the field within such narrow limits. Also larger fields may be employed and heavier dosage given without danger of permanently deleterious effects. In our experience, dosages of 8,000–9,000 r, measured with backscatter, may be employed intravaginally without danger of permanently destructive effects on the mucous membranes, but the contiguous structures, such as bladder and rectum, must be considered. Heavier filtration, in the order of 1 to 2 mm. of copper, is of advantage.

In treating malignant tumors in the accessible surfaces of the mouth and pharynx it is observed that the mucous membrane does not tolerate quite as high dosage as that of the vagina and cervix. Lesions in the mouth, which are frequently secondarily infected, do not usually respond as rapidly, and they may tend to remain necrotic. The factors of bacterial invasion and trauma incident to ingestion of food seem to play an important rôle. Meticulous care in cleansing of the mouth and throat, as well as removal of foci of infection, is imperative.

In the visible or accessible lesions of mucous membrane, periscopic cones of different sizes make it possible to apply roentgen rays in body cavities with accurate placement of the portal and maintenance of position, with immobilization of the patient in a comfortable position.

CASE REPORTS

CASE 1 (Figs. 1 and 2): A 72-year-old man was first seen June 5, 1937, complaining of a "sore beneath the right eye." He stated that it began as a "gathering" one and one-half years prior to admission. It did not grow rapidly. A physician, consulted within three months, applied one small dose of radium by direct contact. The lesion apparently healed but opened up again in a short time. It was excised in May 1936, and remained healed for approximately four months. At this time the first physician began monthly doses of low-voltage unfiltered x-rays (200 r), but without effect.

Figs. 3–5. Case 2: Recurrent lesion on lip (Fig. 3, left) measuring 3 cm. in diameter and 1 cm. in thickness, present for two months, ulcerated and bleeding. It had been treated elsewhere, six years previously, by electrosurgical removal and radium. Biopsy report: squamous-cell carcinoma, grade two. Healing, without scarring, was complete six weeks after high-voltage irradiation. Fifteen months later the patient returned with an edematous, punched-out area on the opposite side of lip (Fig. 4, center). Biopsy: chronic inflammatory lesion. Fig. 5 (right) shows no evidence of recurrence two years later.

On admission, examination revealed a fairly extensive, undermined, invasive ulcer of the right cheek near the inner canthus of the right eye. X-ray examination showed underlying destruction of bone. The biopsy report was epithelioma, grade three.

Nine applications of roentgen therapy were given on alternate days, from June 5 to June 30, with a total dosage of 4,500 r. Due to the obvious depth of extension, it was considered advisable to use heavier filtration—Thoraeus A. The other factors were 200 kv., 40 cm. distance, 4 × 4 cm. field, with careful screening of the eye and adjacent skin.

Subsequent x-ray examination showed regeneration of bone and the lesion has remained healed without scar or other deformity for four years.

CASE 2 (Figs. 3–5): A man of 83 was first seen Dec. 28, 1936, with a sore on the lower lip which he thought was a recurrence after treatment six years previously by electrodesiccation and interstitial radium therapy. He was not certain, however, that the present lesion occupied the same area as the first, which raised a question as to its recurrent or primary character. The patient had been an inveterate pipe smoker and chewed tobacco for many years. The present lesion had appeared two months before we saw him. It was an indurated, ulcerating area on the lower lip to the left of the mid-line, measuring 3 cm. in diameter with an elevation of 1 cm. The microscopic report was squamous-cell carcinoma, grade two. The blood Wassermann was negative. Ten treatments were given on alternate days, with 200 kv., 0.5 mm. copper filtration, 40 cm. distance, screening around the tumor with a 0.5 cm. border of apparently normal tissue. The tumor showed prompt regression and healed within six weeks.

Fifteen months later the patient returned with a punched out, edematous area on the lower lip to the right of the mid-line. The possibility of a malignant growth was considered, but the biopsy report was chronic inflammation. This began to heal after one x-ray treatment of 500 r, but a total dosage of 3,000 r was administered. It is likely that carious teeth were a predisposing factor in this condition.

There has been no evidence of recurrence for over four years.

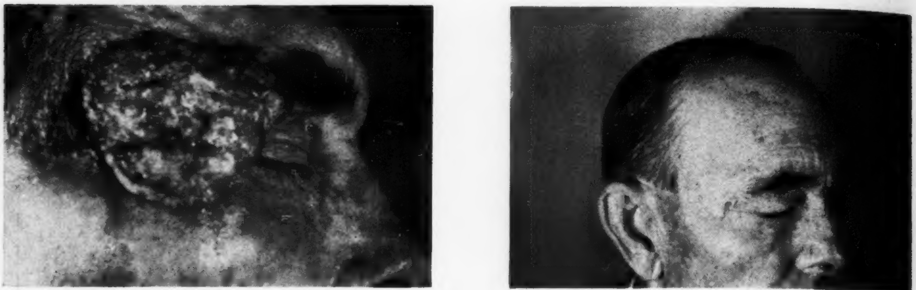
CASE 3 (Figs. 6 and 7): A 60-year-old man was first seen Feb. 27, 1939, with a large, elevated, fungating, ulcerating tumor, measuring 5.5 cm. in diameter on the right temple, and extending to the outer canthus of the right eye. The ulcer bled easily and was secondarily infected. It had appeared at least three years previously as a small "wart," which the patient had tried to remove by repeated applications of castor oil. It had grown rapidly during the last three or four months.

The microscopic diagnosis was epithelioma, grade two. The patient was given eleven treatments of 500 r on alternate days, with a total dosage of 5,500 r. Factors were 200 kv., 0.5 mm. of copper plus aluminum, 50 cm. distance, with a cone and screening of the normal tissue. There was prompt response to irradiation and, in spite of its bulk, the tumor had disappeared within ten weeks, leaving only a scaling roughness about the border of the base. This later disappeared, with little or no scarring and no evidence of residual disease. There has been no indication of damage to underlying tissues. Although only two years have elapsed since this treatment, we believe that all of the viable cells were destroyed.

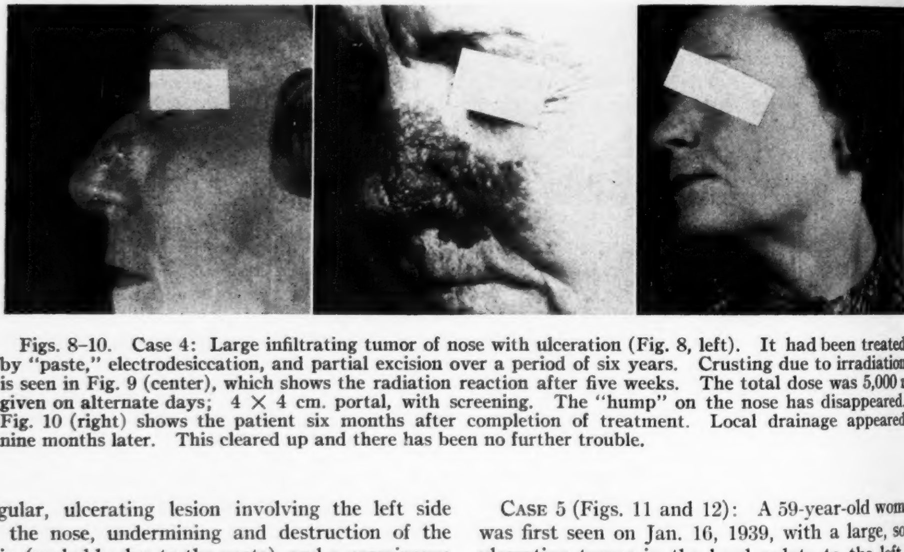
We believe that this tumor represents the maximum in size which should be treated by this technic.

CASE 4 (Figs. 8–10): A woman of 49 years was first seen Dec. 27, 1937, with a "sore on the nose" which was said to have started as a small mole six years before. It had gradually increased in size. Caustic paste had been used; also electrodesiccation and surgical excision. It did not heal, except for short intervals.

When we saw the patient she had an extensive, ir-



Figs. 6 and 7. Case 3: Large cauliflower-like mass on right temple, measuring 5.5 cm. in diameter, ulcerated, bleeding freely (Fig. 6, left), extending to inner canthus of eye. There had been rapid growth for the last three or four months. Biopsy showed epithelioma, Grade II. The bulk of the tumor disappeared two weeks after high-voltage roentgen irradiation, a total of 5,500 r in daily treatments. Fig. 7 (right) shows residual crusts remaining around border of base two months later. These subsequently cleared up with no more treatment.



Figs. 8–10. Case 4: Large infiltrating tumor of nose with ulceration (Fig. 8, left). It had been treated by "paste," electrodesiccation, and partial excision over a period of six years. Crusting due to irradiation is seen in Fig. 9 (center), which shows the radiation reaction after five weeks. The total dose was 5,000 r given on alternate days; 4 × 4 cm. portal, with screening. The "hump" on the nose has disappeared. Fig. 10 (right) shows the patient six months after completion of treatment. Local drainage appeared nine months later. This cleared up and there has been no further trouble.

regular, ulcerating lesion involving the left side of the nose, undermining and destruction of the skin (probably due to the paste), and a prominence of the bridge of the nose, believed to be due to tumor tissue.

She was given a total dose of 5,500 r, in eleven treatments of 500 r on alternate days; factors: 200 kv., 0.5 mm. of copper plus aluminum filter, distance 40 cm. There was considerable skin reaction, which cleared up in eight weeks, leaving the skin intact, without deformity. The "hump" on the nose disappeared.

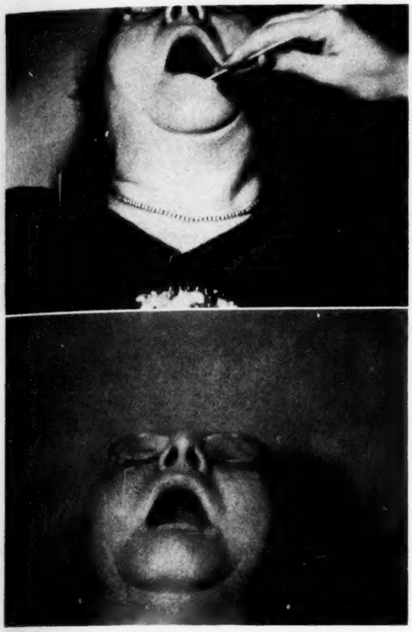
The skin was in good condition until September 1938, when the patient returned complaining of slight drainage from the area treated. In February 1939 this had disappeared, and although the patient has not been in for observation since that time, she reports that she had no recurrence. In our opinion, this flare-up was due to all of the insults to the tissue as a result of past treatment.

CASE 5 (Figs. 11 and 12): A 59-year-old woman was first seen on Jan. 16, 1939, with a large, soft, ulcerating tumor in the hard palate to the left of mid-line. This measured 1.0 × 1.5 × 2.5 cm. It was not tender or painful, and there were no palpable lymph nodes. The pathological report was lymphosarcoma.

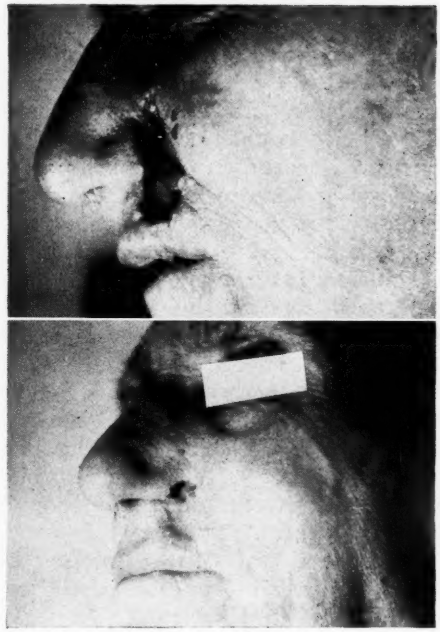
The patient gave a history of "cold sores" in the mouth intermittently for a number of years, which always healed. Two weeks before admission (probably longer) she had another sore, which she thought developed into this tumor.

A total dose of 5,300 r was given through an intracavitary cone, measuring 2.5 cm. in diameter, applied directly to the tumor. The factors were 200 kv., filtration 0.5 mm. of copper plus aluminum, distance 50 cm. Thirteen treatments, 300 r to 500 r per dose, were given at intervals of one to five days.

As we expected, the tumor proved to be very radiosensitive and showed diminution in size during



Figs. 11 and 12. Case 5: Lymphosarcoma of hard palate with ulceration of mucous membrane (Fig. 11, above), 1.5×2.5×1 cm., rapidly growing. Approximately three months after treatment the bulk of tumor was gone (Fig. 12, below), though a slightly depressed area was still present. There was no visible evidence of recurrence and the patient was still symptom-free after an interval of two years.



Figs. 13 and 14. Case 6: Destructive lesion of six years' duration ulceration extending into nose (Fig. 13, above). The lesion—a basal-cell carcinoma—measured 1.5 × 2.5 cm. Fig. 14 (below) shows the patient three months after receiving 5,000 r of high-voltage irradiation given on alternate days. Two years later the lesion was entirely healed; there was still a small opening into nose, but no evidence of activity.

the treatment. Within a few weeks it had entirely disappeared, leaving a small depressed area in the mucous membrane of the palate. Although it has been only two years, the prognosis seems to be good. The patient has had no further trouble and is now wearing an artificial denture without any signs of irritation.

CASE 6 (Figs. 13 and 14): This patient, aged 71, had a destructive lesion on the left side of the face and nose, measuring 1.5 × 2.5 cm. There was a large opening into the naris. The pathological report was basal-cell carcinoma. The lesion had appeared about six years earlier, as a "seed wart." It did not grow rapidly until six months prior to admission. Being a coal miner, the patient had difficulty in keeping it clean.

A total dose of 5,000 r was given, applied locally through a 4 × 4 cm. portal, with screen. The factors were 200 kv., 40 cm. distance, filtration of 0.5 mm. of copper plus aluminum. Treatment was given on alternate days, 500 r per treatment, for a total of ten treatments.

The opening healed slowly with very little scar but was not entirely closed. The skin reaction was minimal.

SUMMARY

Many malignant skin lesions can be destroyed by various destructive agents, provided the technical management is such that the lethal action on the tumor destroys the cells at the base of the growth, as well as those at the periphery, without adversely influencing normal tissue. With roentgen irradiation, the field of exposure must not be too large when heavy dosage is employed.

In our experience, roentgen treatment with high voltage (200 kv.) and medium filtration has given better results, in the more advanced cases, than low-voltage therapy. There have been fewer recurrences, less radiation reaction, more rapid regression of the tumor, and primary healing with less scarring.

Theoretically, the optimum method would be to vary the voltage, filtration, and

distance depending on the thickness of the tumor, but errors in evaluation of actual depth of the extension would result in many failures. Each case, nevertheless, should be individualized. The total dosage should depend on the response of the neoplasm and the reaction of the normal tissues. It is possible to evaluate the dosage better and to prevent undesirable reactions by fractionated treatment.

Although many of our cases have not been observed for a long enough time to be certain of late effects, by employing fields limited in size by careful screening and by directing the beam at different angles to the surface of the skin or mucous membrane, as the case may be, we have avoided to date any perceptible ill effects in the deeper structures.

We believe that there is no selective action in different types of tissue with different qualities of radiation, but a quality produced by 200 kv. and heavier filtration gives a more homogeneous and more effective depth dosage. There seems to be a greater difference between the lethal dose for tumor tissue and normal surrounding tissue with roentgen rays of shorter wavelength.

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Physical and Biological Considerations in the Use of Slow Neutrons for Cancer Therapy[1]

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THE DESTRUCTIVE action of x-rays and fast neutrons on living tissue is known to be due to the action of energetic electrons resulting from the absorption of the x-rays, and of recoil nuclei, especially hydrogen nuclei, which have been projected by neutron impact. The biological action in either case is a result of energy absorption by the tissue from the high-energy, charged particles. The absorbed energy is usually expressed in terms of ionization and, indeed, this is the basis for the physical measurement of the radiation dosage. With either x-rays or fast neutrons, however, the destructive action occurs throughout the irradiated tissue, and no satisfactory method has been found, in the case of cancer therapy, for localizing the damage to the tumor zone. Very often skin damage sets an upper limit to the dose which can be delivered to underlying tissue.

Since the passage of slow neutrons through body tissue is not accompanied by the production of energetic recoil protons, there should be little or no resulting damage from this cause. If, however, these slow neutrons be introduced into a zone which has been perfused with certain chemical elements, such as boron or lithium, or their compounds, nuclear capture reactions will occur which release very energetic particles and result in the local destruction of tissue. That is, for boron:

$${}_5\mathrm{B}^{10} + {}_0\mathrm{n}^1 \longrightarrow {}_3\mathrm{Li}^7 + {}_2\mathrm{He}^4 + 2.5 \text{ MeV}$$

or for lithium:

$${}_3\mathrm{Li}^6 + {}_0\mathrm{n}^1 \longrightarrow {}_2\mathrm{He}^4 + {}_1\mathrm{H}^3 + 4.6 \text{ MeV}$$

Although the energy release is larger for lithium, the probability of neutron capture is much less; thus approximately five times the atomic concentration, or three times the amount by weight, of lithium is needed to obtain the same energy release as with boron. Both reactions are competitive with capture of the slow neutrons by hydrogen and other elements in the body. Small concentrations of boron or lithium are sufficient, however, to capture an appreciable fraction of the neutrons.

The foregoing considerations suggest an investigation of the applicability of neutron-boron or neutron-lithium technics to the localized treatment of tumors. The method would be based on the introduction of boron or lithium compounds into the tumor region and the subsequent irradiation of this region with slow neutrons. The neutron-capture reactions would then result in localized damage to the tumor.

In the following sections, experimental work is described dealing with various methods of introducing the neutron-capturing materials into tumor tissue prior to irradiation with slow neutrons. Also, physical and biological principles have been elaborated to serve as a guide for further experimentation.

EXPERIMENTAL

Kruger (1940) has demonstrated the effectiveness of the boron-slow neutron process. He immersed transplantable tumor fragments in boric acid prior to irradiation *in vitro* with slow neutrons. Fragments so treated when implanted into

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[3] The Haskins Laboratories, New York City.

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host mice "took" with less frequency than those treated with boric acid or slow neutrons alone.

The authors were independently testing the effectiveness of the boron-slow neutron process *in vivo*. Zahl, Cooper, and Dunning (1940) injected growing mouse sarcomas with various forms of slow neutron-capturing materials. When the whole animal whose tumor was so injected was irradiated with slow neutrons, a significant increase in tumor regression was observed. This increase was attributed to the localized ionization resulting from the nuclear disintegration products of the capture process.

One of the interesting aspects of this work was that, while in x-ray cancer therapy shielding of tissues not under treatment must be carefully applied, here it was possible to subject the whole body to the same extrinsic energy as the tumor, but, because of the boron-slow neutron process, there was set up a high ionization differential between the tumor and the rest of the body.

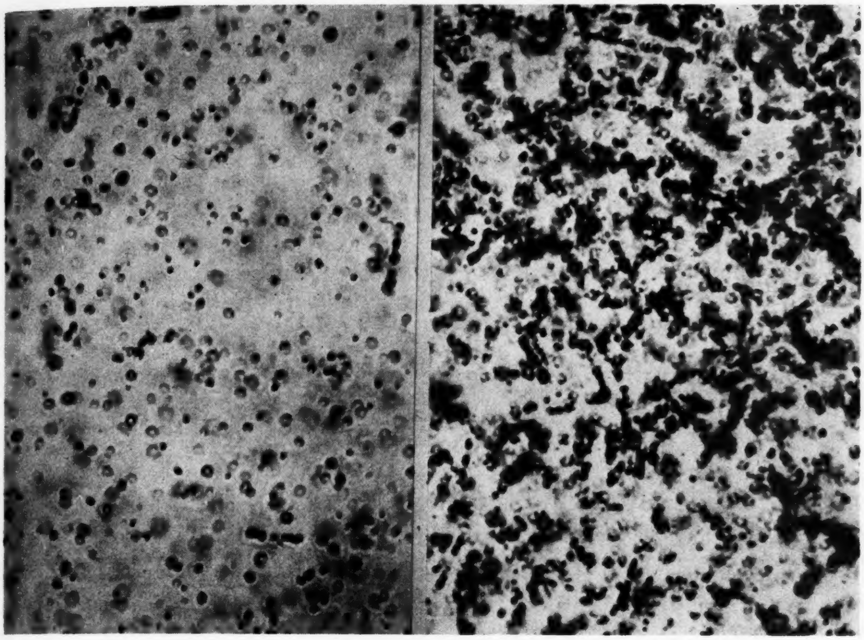
In connection with this work, however, it was pointed out that the method of direct hypodermic injection of slow neutron-capturing materials into the tumor area does not seem clinically feasible, first because of the liability of metastasis production following mechanical entry of the needle into the tumor and, in the second place, because of the peculiar selective permeability properties of the living cell membrane; it is difficult to believe that after the injection of boron or lithium solutions into or around a tumor mass, uniformly high concentrations could be maintained both within and out of the malignant cells, particularly in the case of large and involved or deeply situated growths. The authors suggested that for any possible future employment of the boron-slow neutron process in tumor therapy, some device other than simple hypodermic injection should be developed for localizing either boron or lithium, or related materials, in malignant tissue.

The possibility of selective localization in malignant tissue of slow-neutron-capturing materials through the medium of intravenous injection was suggested by the work of Ludford (1929), Duran-Reynals (1939), and others, who observed that certain acid dyes, when introduced into the blood stream, would accumulate in greater concentration in tumor tissue than in normal tissue. Since most of such localizing dyes are sodium salts of the azo-sulphonic acid complex, it was hoped that by substituting lithium atoms for the sodium atoms which are normally present in the dye-salt molecule, the dye molecule would act as a vehicle for localizing lithium (which was used instead of boron because of its chemical similarity to sodium) in the malignant tissue.

Lithium salts[4] of pontamine sky blue 6B, trypan blue, and carminic acid were prepared and injected intravenously both into mice bearing spontaneous mammary tumors and mice bearing implanted tumors of the sarcoma 180 strain, although it was observed that tumors of these two types behave similarly in respect to the experiments here presented.

Lithium carmine is a dye of old and classical usage. It is relatively non-toxic, a 25 gm. mouse easily tolerating from 0.5 to 1.0 c.c. of a 2.7 per cent aqueous dye solution slowly injected intravenously. Although the toxicity of lithium pontamine sky blue 6B and lithium trypan blue was not precisely determined, they were used in about the same concentration as the lithium carmine without observable ill effects on the animal. It may be mentioned that the lithium pontamine sky blue 6B was found by test to be five times stronger tinctorially than sodium pontamine sky blue 6B. As a consequence, the entire animal following injection with the lithium pontamine sky blue 6B, in the concentrations mentioned, becomes diffusely and deeply colored, any color differential between tumor and body tissue being almost obliterated. When much smaller amounts

[4] Grateful acknowledgment is made to the Dyestuffs Division of E. I. du Pont de Nemours & Company and to the National Aniline and Chemical Company for the preparation of the lithium salts of their dyes.



Figs. 1 and 2. Ionization produced in regions without and with boron when bombarded with slow neutrons. It is the ionization differential illustrated in these two photographs which presents the basic rationale of the experiments discussed in the text.

Fig. 1 (left): Without boron. Eastman alpha particle spectroscopic plate exposed to slow neutron irradiation. Three tracks due to protons projected by neutrons are clearly visible in the field, together with general photographic grain reduction due to protons projected at various angles to the plane of the plate, together with projected nuclei such as carbon, and to gamma-ray background. This illustrates essentially the amount of ionizing energy released in an equivalent volume of hydrogen-rich tissue during an equivalent period of irradiation. × c. 1500.

Fig. 2 (right): With boron. Same type of plate and same exposure time as Fig. 1, except that emulsion before exposure was dipped into a 2.0 per cent aqueous solution of boric acid and allowed to dry. Numerous alpha particle tracks are seen, resulting from slow neutron-boron capture. Many tracks do not lie in the plane of the photograph. This illustrates essentially the amount of ionizing energy released in an equivalent volume of tumor tissue containing boron.

are injected, the color differential again becomes easily observable. The color in the case of the blue dyes persists for several weeks, whereas the coloration caused by the lithium carmine appears to decrease in intensity more rapidly, body color becoming quite normal about ten days after injection.

The question of the precise cytological location of the dye within the tumor is important from the point of view of neutron therapy. Considering the range of penetration through tissues of the alpha particles and protons which result from the lithium-slow neutron disintegration as from ten to forty microns, it seems essential that localized lithium must be close to the growing malignant cells. Macroscopic observations on large rat and mouse sarcomas from animals previously treated with lithium carmine reveal that the peripheral zone is most heavily dyed. If this zone is assumed to be the band of actively growing malignant cells normally found in the periphery of a tumor, then one would assume that the dye was being localized in a most advantageous position. Further studies (1941) to determine the precise cytological position of the dye and the lithium are now under way.

After suitable periods following intravenous injection of the dyes, animals were sacrificed and tumor and other tissues removed and analyzed spectroscopically for

lithium content. Most complete data were taken in the case of the lithium carmine experiments, and therefore only these will be presented in detail.

The results of such studies are presented graphically in Figure 3. It is seen that the maximum concentration of lithium in the tissue is attained during the four- to seven-hour period after injection. It is seen further that the percentage of elemental lithium in tumor tissue is considerably higher than in the other tissues assayed.

comes relatively independent of the dye molecule. It is necessary, therefore, to assume that the bonding between the lithium atoms and the dye molecule is such as to permit a type of displacement or hydrolysis to occur within the body, releasing the lithium as an independent ion.

If it is true that the dye molecule and the lithium atoms become physiologically or chemically independent of each other, one may reasonably inquire as to whether or not the lithium ion alone exhibits a pref-

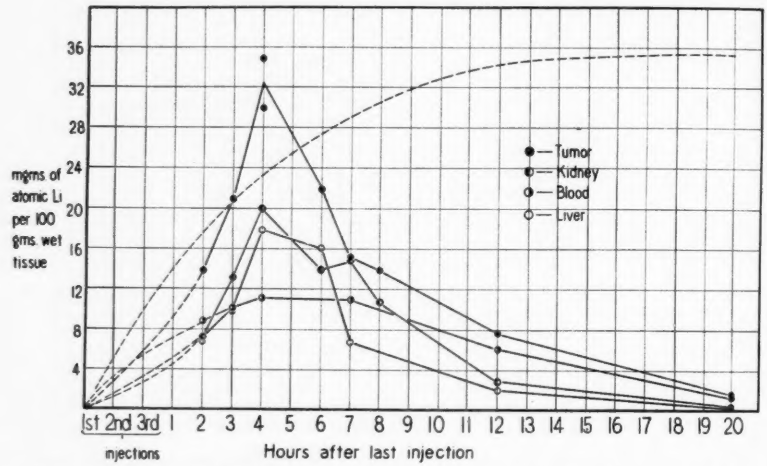


Fig. 3. Content of elemental lithium in various tissues following intravenous injection of lithium carmine. Three injections of one c.c. each of a 2.7 per cent aqueous solution of lithium carmine were made at half-hour intervals. Animals were sacrificed at suitable periods following last injection. Total amount by weight of elemental lithium injected was in the order of 3–5 mg. The broken line represents a qualitative estimate of tumor color density as a function of time.

Before considering the significance of this differential, certain other correlative experiments must be presented.

It is seen in Figure 3 that twenty-four hours after injection of lithium carmine, elemental lithium is no longer spectroscopically detectable in the tissues. It was observed, however, that following injection of the lithium dye, the coloration of the tissues persisted for many days. The broken-line curve in Figure 3 is a qualitative statement of the color intensity of the dye in tissues as a function of time. From a comparison of the lithium curves and the color curve, it seems that the physiological behavior of the lithium be-

erential localization in tumor tissue over that of the other tissues assayed. To test this, aqueous lithium chloride solutions were injected intravenously into tumor-bearing mice in the same manner as the lithium dye solutions. Spectroscopic assays were made on tissues of animals so treated. These assay data are presented in Figure 4-II. Again a higher percentage of lithium was found in the tumor tissue of such mice than in the liver and blood, although the concentrations in the tumor and kidney differed only by a small amount. Figure 4-I reports an experiment in which the same total amount by weight of elemental lithium was injected

in the form of lithium chloride and lithium carmine. Here the differential between tumor and normal tissue is somewhat higher than in the case of Figure 4-II, but it is difficult to say whether the difference in the results of these two experiments is significant. Such localization of a metallic ion in malignant tissue or in lesions is not wholly unique. Menkin (1940) has reported a localization of iron in lung tubercles following intravenous injection of ferric chloride into tuberculous rabbits. from general toxemia. In the experiments of Figures 3, 4-I, and 4-II the amount of material injected was near the tolerance limit.

It is not within the scope of this paper to discuss the mechanics or physiology of the localization of lithium or other materials. An entire literature exists on the selective passage of ions or dye molecules through living membranes. Rather, an attempt has been made to determine whether a differential localization of lith-

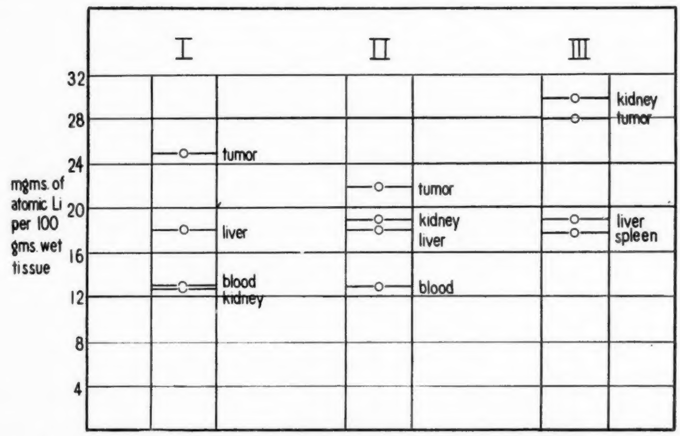


Fig. 4. I. Animal injected with lithium chloride and lithium carmine in amounts such that both materials contributed equally to lithium. Dose adjusted so that total amount of elemental lithium injected would be in the order of 3–5 mg.

II. Animal injected with lithium chloride in the same manner as in I. Dose adjusted so that total amount of lithium injected would be in the order of 3–5 mg.

III. Animal injected with lithium chloride repeatedly over several hours, so that total amount of lithium was in the order of 10–20 mg.

Duran-Reynals (1939) has made similar observations on the localization of foreign proteins in mouse tumors. Investigations by Woodard (1940), and earlier workers, also indicate a localization of phosphorus and metallic colloids in tumor tissue.

It is of interest to note in Figure 4-III that, if large and persistent doses of lithium chloride are injected into the mouse, the concentration differential between the tumor and the kidney, at least, is considerably lessened; also the absolute amount of lithium in the tumor is not greatly increased. The amount of lithium chloride used in this case would probably have resulted in the early death of the animal ium or boron compounds could be attained, and in a concentration sufficient to induce a greater destruction of malignant tissue than of surrounding normal tissue, when an area so treated is irradiated with slow neutrons.

PHYSICAL AND BIOLOGICAL CONSIDERATIONS

In order to estimate the biological effects resulting from the capture of slow neutrons by boron or lithium which have been localized in a tumor region, it is necessary to consider the physical processes in some detail. The slow neutrons supplied to the tumor and surrounding tissues are ultimately captured either by

the elements composing the tissue or by the added compounds of boron or lithium. The fraction of the neutrons captured by each element is dependent on its capture cross-section and on the number of its atoms present (Livingston and Bethe, 1937; Lapointe and Rasetti, 1940). The distribution of the neutrons which results from the addition of small amounts of boron or lithium to tissue is shown by the two lower curves of Figure 5. The ordinates represent the percentage of the available slow neutrons[5] which are captured by boron or lithium; the abscissae show the concentrations of these elements, as per cent, by weight of wet tissue.[6] The upper two curves of Figure 5 apply to the isotopes[7] B^{10} and $Li.^{6}$ It is obvious that the use of these isotopes would permit the capture of a larger fraction of the neutrons without the necessity of increasing the chemical concentration. Also, the curves show that for neutron capture, boron is much more effective than lithium, though the advantage largely disappears if the isotopes are to be used.

Since the purpose in capturing the slow neutrons is to make available the nuclear reaction energy for cellular destruction, it is next of interest to compare the amounts of energy made available by the addition of boron and lithium to the tissue in various concentrations. Figure 6 shows the energy absorbed by the tissue as a function of the concentrations of boron, lithium, and their active isotopes. The

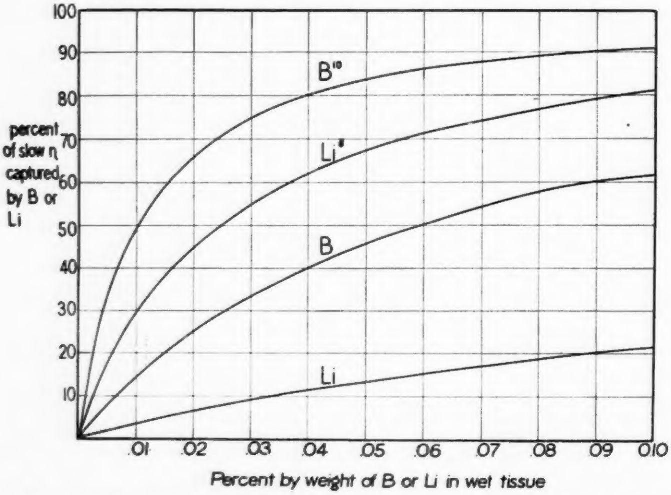


Fig. 5. Per cent of slow neutrons captured by boron or lithium or their isotopes when one of these is introduced into "average" (see footnote 6) wet tissue in varying concentration.

[5] For simplicity it is assumed that the slow neutrons are supplied and utilized uniformly throughout the irradiated region. In individual cases the neutron distribution will depend on the irradiation conditions and geometry. Further, the boron or lithium in the tumor zone will to some extent drain neutrons from adjacent irradiated regions. This effect also depends on the size and shape of the tumor zone, and may, under certain conditions, contribute significantly to the radiation dose in the tumor.

[6] For the purposes of this calculation, the composition of tissue was taken as the average composition of the human body as a whole: Oxygen, 63.03%; carbon 20.20%; hydrogen, 9.90%; nitrogen, 2.50%; calcium, 2.50%; phosphorus, 1.14%; chlorine, 0.16%; fluorine, 0.14%; sulfur, 0.14%; potassium, 0.11%; sodium, 0.10%; magnesium, 0.07%; iron, 0.01%. These data are cited by M. Bodansky: Introduction to Physiological Chemistry, New York, Wiley & Sons, Inc., 2nd Edition, 1930, p. 6.

[7] As indicated by the equation on p. 673 only the boron isotope of mass 10, *i.e.*, B^{10}, is implicated in the capture of slow neutrons by boron. Since B^{10} atoms comprise only 18.4 per cent of atoms making up the chemical element boron per unit weight, the "undiluted" B^{10} atoms are 5.5 times as effective as boron in capturing neutrons. Similarly Li^{6} is 12.7 times as effective as lithium.

These isotopes are not at the moment available in the quantities necessary for the use indicated, but this condition will not necessarily continue to hold.

energy, however, does not become zero at zero concentration because there are neutron reactions with some of the elements in normal tissue, especially hydrogen, nitrogen, chlorine, and phosphorus. These reactions liberate a considerable amount of energy, but much of it is in the form of penetrating gamma radiation, and only a small fraction of this is absorbed locally. The reaction with nitrogen, however, and the radioactive decay of chlorine and phosphorus yield ionizing particles whose energy is completely absorbed at the site of the reaction. The total energy[8] absorbed by the tissue and due to capture of all the slow neutrons by normal tissue constituents is shown by the horizontal line in Figure 6.

The addition of boron or lithium results in a net increase of absorbed energy only because more energy is made available when a neutron is captured by boron or lithium than when the neutron is captured by elements of the tissue, usually hydrogen. Since the energy released following capture by lithium is nearly twice that by boron, it is not surprising that the advantage of boron over lithium as shown in Figure 6 is much less than in Figure 5. In the case of the isotopes, Li^6 provides considerably more energy than B^{10}.

It is evident from Figure 6 that increasing the amount of boron or lithium in tissue will continuously increase the total energy absorbed. It is not the total energy absorbed, however, but rather the difference in energy between tumor and healthy tissue, which determines the optimum treatment condition. This differential dose should be made as large as possible; the absolute amount of the dose can then be adjusted by varying the quantity of slow neutrons administered. In any practical case it would hardly be possible to restrict the added materials entirely to the desired region, *i.e.*, the tumor. Rather there will always be boron or lithium in some concentration throughout the region exposed to the slow neutrons. The difference in the radiation dosage supplied to the tumor and to the surrounding tissue, *i.e.*, the dose differential, will therefore depend considerably on the difference in concentration of boron or lithium in the tumor region and in the adjacent tissues. The ratio of these concentrations, which we have called the localization factor,

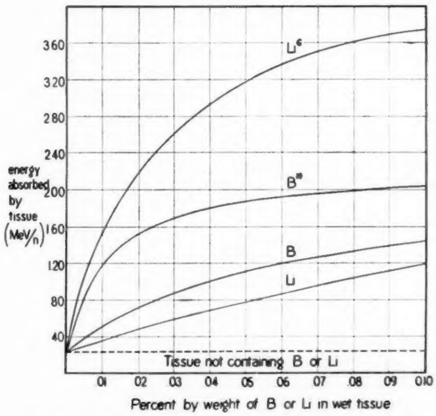
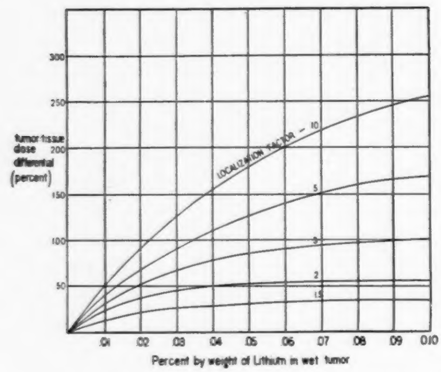
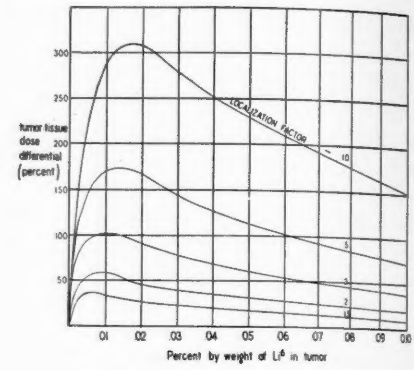


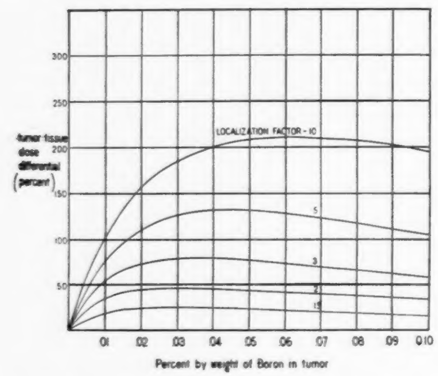
Fig. 6. Energy absorbed by tissue containing varying amounts of boron or lithium or their isotopes. The energy is supplied by slow neutron capture reactions with these elements and with constituents of the tissue.

is not, however, the only consideration. The dose differential depends also on the absolute quantity of added material and, in fact, passes through a maximum as the quantity of boron or lithium is increased. In Figures 7, 8, 9, and 10 are shown the dose differentials presented as a function of the concentration of lithium, boron, Li^6, and B^{10}, and for various values of the localization factor. It is evident that if the localization factor is comparatively small, *i.e.*, 1.5 to 2, it might be quite feasible to use concentrations of lithium or boron for which the differential dose is almost, if not actually, as great as could be obtained even with the separated isotopes. The differential dose in these cases is not unusually large but is substantial. If, how-

[8] In the calculation of the total energy absorbed by tissue, the chemical composition of the tissue is the same as before (footnote 6). This will not correspond to individual cases involving tissues whose actual chemical composition differs from the above average. Such cases require individual treatment. The calculation of the fraction of the gamma-ray energy utilized (5.5 per cent) involved an arbitrary assumption about the raying geometry: slow neutrons were assumed to impinge on a circular area of 5 cm. diameter.







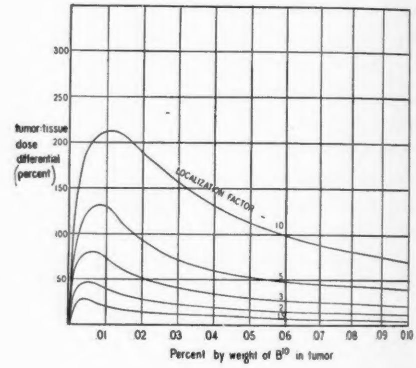


Fig. 7 (above). The per cent by which energy absorbed in tumor tissue exceeds that absorbed in normal tissue as a function of the concentration of lithium in the tumor tissue. The parameter is the ratio of lithium concentration in the tumor tissue to that in the normal tissue.

Fig. 8 (below). The per cent by which energy absorbed in tumor tissue exceeds that absorbed in normal tissue as a function of the concentration of boron in the tumor tissue. The parameter is the ratio of boron concentration in the tumor tissue to that in the normal tissue.

Fig. 9 (above). The per cent by which energy absorbed in tumor tissue exceeds that absorbed in normal tissue as a function of the concentration of Li^6 in the tumor tissue. The parameter is the ratio of Li^6 concentration in the tumor tissue to that in the normal tissue.

Fig. 10 (below). The per cent by which energy absorbed in tumor tissue exceeds that absorbed in normal tissue as a function of the concentration of B^{10} in the tumor tissue. The parameter is the ratio of B^{10} concentration in the tumor tissue to that in the normal tissue.

ever, the localization factor is larger, the differential dose becomes quite favorable. Also for this case, and at rather low concentrations, there is a definite advantage of boron over lithium and of Li^6 over either boron or B^{10}.

From the data of Figure 3 the experimental work done thus far has attained a localization factor of approximately 2.0 and a maximum concentration of approximately 0.03 per cent lithium in the tumor. This corresponds to a gain of about 43 per cent in the radiation dosage of the tumor over that of the other tissues in the same mouse. There should be no difficulty in utilizing the isotope, Li^6, if it were available. In this case the gain would be about the same, but lower concentrations could be used with advantage.

It would seem, from a consideration of Figures 7–10, that the most profitable course of experimentation might be one designed to increase the localization factor as much as possible. This is evidently of more advantage than increase in the total concentration. Furthermore, the studies should include both boron and lithium. The former has advantages, especially at low concentrations, but a technic for lithium, if used with the Li^6 isotope,

would give very large dose differentials. There is the further possibility that the uranium isotope, U^{235}, might sometime be available and physiologically usable. The energy release per neutron in this case is extremely large.

A factor, not thus far considered, which may improve the dose differential as measured by biological rather than physical effects is the ionization density caused by the various particles. The energy resulting from neutron capture by boron or lithium is absorbed by the tissue from heavy, densely ionizing particles; that from neutron capture by elements of the tissue is absorbed from fast electrons which do not ionize densely. While the relations between biological damage and density of ionization along the path of a particle are not clearly understood, there are a number of experiments (Zirkle, 1937; Lawrence, 1937; *et al.*) which have been interpreted as showing that the biological effectiveness of heavy particle ionization is greater than that of electrons by a factor ranging from two to five. If such a factor is found to apply to the case of tumor irradiation, the effect would be to increase considerably the differential doses shown in Figures 7, 8, 9, and 10 when these are converted from physical to biological equivalents.

The physical and biological considerations of this section apply directly to technics which might be developed for the treatment of tumors that lie near the surface, thereby permitting the ready penetration of slow neutrons throughout the tumor zone. These considerations also apply to the treatment of deep-seated tumors by a beam of fast neutrons, since they form the basis for an auxiliary technic to utilize the slow neutrons resulting from the slowing down of fast neutrons of the beam. The possibility, not existent with x-rays, of thus securing an increment of ionization localized at a tumor containing boron or lithium provides one of the important reasons for considering the potentialities of fast neutron therapy in conjunction with slow neutron effects.

SUMMARY AND CONCLUSIONS

(1) It is pointed out that in conventional x-ray cancer therapy no wholly satisfactory method has been found for localizing tissue destruction to the tumor zone. Skin damage often sets an upper limit to the dose which can be delivered through the skin to underlying tissue. On the other hand, little destructive ionization is produced when slow neutrons pass through body tissue unless that tissue is perfused with such chemical elements as boron or lithium or their compounds. If the concentration of such neutron-capturing materials is sufficiently high, disintegration products of the capture process may give rise to a destructive ionization wherever such materials are found. For therapy such materials should be localized in the tumor mass.

(2) Various agencies for localizing boron and lithium are discussed. The agency holding greatest promise appears to center around the property of tumor tissue selectively to localize intravenously injected materials, notably certain organic dyes. Azo and related dyes, which are normally sodium salts, were prepared in which the sodium atoms were replaced with atoms of lithium. Such dyes were injected intravenously into tumor-bearing mice, and it was observed on spectroscopic assay that higher concentrations of lithium could be attained in tumor tissue than in other tissues of the same animal. Furthermore, the total concentration of lithium was sufficiently high to indicate that irradiation with slow neutrons would result in a considerable ionization differential between tumor and normal tissue, favoring tumor destruction.

(3) The relation between absolute concentration of slow-neutron-capturing materials and the differential concentration of these materials in tumor tissue and normal tissue is described and discussed. In view of the concentrations attained by experiments on mice, suggestions are made as to the most suitable forms of slow-neutron-capturing materials to be used. It is indicated that, before clinical

application of the slow neutron concept be made, efforts should be directed toward developing methods for increasing the concentration differentials of these materials.

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Tracer Studies with Radioactive Phosphorus in Malignant Neoplastic Disease[1]

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The success of Lawrence and his co-workers (1, 2) in the treatment of leukemia with radioactive phosphorus (P^{32}) suggests that this isotope may also be of value in the treatment of certain malignant neoplasms. In order to obtain knowledge as to the immediate deposition of P^{32} in cancer tissue, small amounts of this isotope, about 0.5 microcurie, in the form of a 1.5 to 3.0 per cent solution of Na_2HPO_4, have been administered at varying times before operation to patients with the following operable neoplasms: carcinoma of the breast, osteogenic sarcoma, lymphosarcoma.

Small portions (about 2 grams) of the different tissues in the surgically excised specimens were weighed to 0.5 milligram, ashed at 500° C., and their radioactivity determined by direct comparison with accurately measured fractions of the original solution given to the patient. The final values were expressed in terms of microcuries per kilogram of tissue and were corrected for decay to the date of administration of the P^{32}. Specimens with activities of 0.1 microcurie or less were measured with a Geiger counter, and those with activities of more than 0.1 microcurie were measured with a Lauritsen electroscope. Specimens which had a large amount of ash were suitably subdivided to prevent error due to absorption of the beta rays by the ash.

It is to be expected that the concentration of the isotope in tissues after such "tracer doses" is representative of concentrations to be found after the administration of therapeutic amounts of the isotope, provided the difference between the amounts of phosphate administered in each instance is not too large.

In order that proper account could be taken of the variable weights of patients and the differences in the amounts of isotope administered, the concentration of P^{32} in tissue, expressed in microcuries of P^{32} per kilogram of tissue, was divided by the microcuries of P^{32} administered per kilogram of body weight. The resultant figure was termed the "differential absorption ratio"[3] (D.A.R.). When this is done a ratio is established between the amount of phosphorus actually absorbed by that tissue and the amount it would have contained if the isotope had been equally distributed throughout the whole organism. This ratio shows at once whether a neoplastic tissue absorbs an amount of the isotope sufficiently above the average for the entire body to make it a potentially useful method of therapy. If, for example, a neoplastic tissue has a differential absorption ratio of 1, it will receive no more radiation from the radioactive phosphorus than will the whole body. On the other hand, if the ratio were 6, it would receive 6 times as much radiation as the average body tissue. In the first instance, P^{32} would be expected to be of little value; in the second instance, it could be of significant therapeutic effect.

The ratio has been based on the *administered* dose rather than the *retained* dose, because in many instances it was not possible to measure the excretion of the isotope. This method is satisfactory, because the usual range of excretion of the ad-

[1] From the Memorial Hospital, New York. Read before the Radiological Society of North America at the Twenty-sixth Annual Meeting, Cleveland, Ohio, Dec. 2-6, 1940.

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[3] For example: If an adult of 70 kilograms is given 0.5 millicurie (500 microcuries) of P^{32}, the administered dose is 7.2 microcuries per kilogram of weight (500/70). If, then, in this same patient a tissue absorbs 14.4 microcuries per kilogram, corrected for decay to the date of administration of the P^{32}, the differential absorption ratio is 14.4/7.2 or 2.

TABLE I: DIFFERENTIAL ABSORPTION RATIO OF RADIOACTIVE PHOSPHORUS FOR PATIENTS WITH CARCINOMA OF THE BREAST

Case Number	Microcuries P^{32} Administered per Kilogram of Body Weight	Days Between Administration of P^{32} and Operation	Differential Absorption Ratio: Primary Tumor	Breast Tissue	Metastatic Node	Normal Node	Muscle	Fat	Skin	Blood
44551	5.6	1	1.3	0.2	...	1.8	0.7	0.2	0.3	0.8
59863	4.9	2	0.8	0.4	...	2.4	0.8	0.1	0.3	0.7
59714	2.6	5	1.9	0.3	3.3	2.5	1.2	0.2	0.5	0.5
59935	5.4	5	0.8	0.2	...	1.3	0.9	0.1	0.2	0.3
59995	9.1	5	...	...	4.0	2.8	1.3	0.1	0.4	0.4
59998	5.5	5	1.6	0.3	3.6	1.6	1.0	0.1	0.5	0.1

ministered dose is between 10 and 25 per cent, a variation not great enough to alter the ratios significantly. Admittedly, the ratio may be different on different days for the same tissue in the same patient. This can be compensated for by making observations on a large group of patients at different intervals after the administration of a tracer dose of P^{32}. It is also realized that the ratio can probably be decreased or increased to some extent by varying the total amount of phosphorus[4] administered. In all of these tracer studies, however, this did not exceed 10 per cent of the average patient's daily intake of 1 gram of phosphorus.

Table I presents the results of the analysis of tissues from patients with breast carcinoma; Table II with osteogenic sarcoma; Table III with lymphosarcoma.

If the concentration of the radioactive phosphorus in a tissue is known, it is possible to estimate the radiation dose delivered to that tissue by the isotope. Through suitable formulae which take into account the energy of the beta ray, the number of disintegrations per second, and the half life, this dose can be expressed on an ionization basis to correspond closely to doses delivered with x-rays. For convenience, doses thus determined are expressed in "roentgen equivalents" (3). One such formula shows that if 1.1 microcuries[5] of $_{15}P^{32}$ remain in a kilogram of tissue until it has completely disintegrated, 1 "roentgen equivalent" of radiation will be delivered to that tissue. This value can be combined with the differential absorption ratio of any tissue to determine the probable maximum radiation that might be delivered to that tissue by any administered dose of this isotope.[6]

CARCINOMA OF THE BREAST[7]

This lesion was selected for study primarily because its frequency made available a sufficient number of cases in a relatively short time. A further reason was that the figures obtained from the study of this type of neoplasm should indicate to some degree what absorption of the phosphorus would take place in other types of carcinoma.

It can be seen from Table I that the D.A.R. for the primary tumor ranged from 0.8 to 1.9, and for uninvolved breast tissue from 0.2 to 0.4, and that the isotope

[4] It is to be remembered that when radioactive phosphorus, P^{32}, is administered, a much larger amount of non-radioactive phosphorus, P^{31}, is administered at the same time. The ratio of atoms of P^{32} to P^{31} in the solution is about 1 to 10,000,000.

[5] 1 microcurie equals 0.001 millicurie.

[6] For example: If the administered dose is 100 microcuries per kilogram of body weight and ratio for a tissue is 3.3, then that tissue would absorb 330 microcuries (3.3 × 100). The roentgen equivalent dosage is obtained by dividing 330 by 1.1, in this case 300.

[7] These patients were from the service of Dr. Frank E. Adair.

TABLE II: DIFFERENTIAL ABSORPTION RATIO OF RADIOACTIVE PHOSPHORUS IN PATIENTS WITH OSTEOGENIC SARCOMA

			Differential Absorption Ratio							
Case Number	Microcuries P^{32} Administered per Kilogram of Body Weight	Days P^{32} Administered Before Operation	Primary Tumor	Primary Tumor	Primary Tumor	Femur	Tibia	Muscle	Epiphysis	Remarks
62057	7.3	1	5.8	1.7	1.1	0.7	0.6	0.7	...	Heavy irradiation 6 mo. before operation
61190	9.7	2	4.6	1.0	0.6	0.4	...	0.7	...	No preop. irradiation
59700	2.2	3	3.1	...	...	...	0.8	1.9	1.5	No preop. irradiation
59044	7.6	5	8.3	4.0	2.4	1.7	...	0.9	...	Heavy irradiation 2 wk. preop.
59202	41.0	7	2.6	...	...	0.4	...	0.2	0.7	Heavy irradiation 2 wk. preop.

uptake in the neoplasm was from 2 to 7 times that of normal breast tissue. There is little reason, however, to expect that radioactive phosphorus could be used for primary therapy in this disease. A dose of 500 microcuries per kilogram of body weight, administered over a period of time, would provide as a maximum only between 450 and 1000 r to the primary tumor. This dose of the isotope is about as great as can be safely administered to an adult of 70 kilograms weight and would probably provide about 300 r whole body radiation. Lymph nodes which contained metastatic foci had a D.A.R. of 3.3 to 4.0, whereas normal lymph nodes ranged from 1.3 to 2.8. In the individual case the uptake ratio between these two tissues varied from 1.3 to 2.2. The hypothetical dose mentioned above would deliver to the diseased nodes between 1,000 and 2,400 r tumor dose, and to the normal nodes between 800 and 1700 r. The higher absorption by the metastatic areas suggests that the radioactive phosphorus might be a useful therapeutic adjunct in patients who are to be treated by x-ray.

OSTEOGENIC SARCOMA[8]

Phosphorus is a normal constituent of bone, whose metabolism is in a large degree controlled by an alkaline phosphatase (4). Many osteogenic sarcomas are rich in this enzyme (4), a fact which is often reflected by a high serum phosphatase. The phosphatase in the tumor increases the need of that tissue for phosphorus. It seemed likely, therefore, that radioactive phosphorus would be absorbed by osteogenic sarcoma in sufficiently large quantities to make it a useful therapeutic agent.

It can be seen from Table II that the D.A.R. for the primary tumor varied from 0.6 to 8.3, and for shaft of normal bone from 0.4 to 1.7. In the individual case the uptake ratio between these two tissues ranged between 1.2 to 1 and 10 to 1. Those portions of the tumor with the lowest absorption ratio were regions in which the tumor was hemorrhagic or had otherwise degenerated, areas which as a rule were relatively poor in phosphatase. The areas most actively growing, as indi-

[8] These patients were from the service of Dr. Bradley L. Coley.

TABLE III: DIFFERENTIAL ABSORPTION RATIO FOR RADIOACTIVE PHOSPHORUS IN PATIENTS WITH LYMPHOSARCOMA

Case Number	Micro-curies of P^{32} Adminis-tered per Kilogram of Body Weight	Days Be-tween Ad-ministra-tion of P^{32} and Biopsy	Differential Absorption Ratio Lymph Node	Blood
N-9373	10.2	1	10.0	0.6
N-9863	9.2	2	4.6	0.5
O-1380	6.0	2	2.6	..
M-8614	1.7	5	4.2	0.8
N-511	9.6	5	3.1	0.5
N-3342	5.5	6	2.4	0.3
N-9526	7.8	8	3.9	..
N-1796	4.7	8	3.1	0.3
N-6776	13.3	11	2.2	..
N-4354	12.6	13	4.5	0.3
N-5336	7.0	31	12.0	0.05

cated by a relatively high enzyme content, were the ones with the highest absorption ratios. If, however, we use the figure 4 as an over-all average absorption ratio for the primary tumor, for a dose of 500 microcuries per kilogram of body weight, it would receive about 2,000 roentgen equivalents tumor dose, too little to provide a primary method of therapy (4). If, however, the only method of therapy to be used is x-radiation, the administration of this amount of the isotope would provide the advantage of at least a 30 per cent increase in the usual roentgen tumor dose, which in osteogenic sarcoma does not usually exceed 6,000 to 7,000 r.

LYMPHOSARCOMA[9]

Table III presents the results of the analysis of the tissues examined in patients with lymphosarcoma.

The D.A.R. for lymph nodes showing lymphosarcoma varied from 2.2 to 12.0. Because these patients were subjected only to local biopsy of a diseased node, no ratios for normal tissues are available for comparison.

The two highest ratios, 10.0 and 12.0, were observed in patients in whom biopsy was done on the first day and on the 31st day after receiving P^{32}. Exclusive of these two patients, the ratio varies from 2.2 to 4.6, with a general average of about 3. If an arbitrary dose of 300 microcuries per kilogram of body weight were administered over a period of time, the average lymphosarcoma tissue with a differential absorption ratio of 3 would absorb 900 microcuries per kilogram, an amount which would eventually deliver a tumor dose of about 800 roentgen equivalents, if none of the absorbed isotope were excreted by that tissue. This amount of P^{32}, 300 microcuries per kilogram, should be well tolerated by the average adult in good general condition, provided that it is not administered in too short a period of time. Experience with x-rays has demonstrated that lymphosarcoma tissue often regresses completely with tumor doses of 600 roentgens or less. It seems, therefore, that radioactive phosphorus should offer a very effective method of therapy in this disease. The duration of treatment, however, is a matter of days in x-ray therapy, whereas it is a matter of weeks in P^{32} therapy. Therefore, this conclusion may not necessarily prove true.

It is to be noted that for the different patients there is a marked variation in the ratio, which apparently is neither related to the amount of P^{32} administered nor to the interval between administration and biopsy. Inasmuch as the absorption ratio, and possibly its relationship to time, is apparently individual, it would seem best, if it is proposed to treat a case of lymphosarcoma with P^{32}, to administer a tracer dose of the isotope and perform a biopsy about fourteen[10] days later. If the ratio is good at that time, *i.e.*, 3 or better,[11] the patient should be expected to show good therapeutic response.

[9] These patients were from the service of Dr. Lloyd F. Craver.

[10] The ratio at this time should roughly indicate the average dosage ratio for the full period of effective irradiation from the P^{32}.

[11] It is to be emphasized that, in calculating the ratio, the measured radioactivity is corrected for decay to the date of administration of the P^{32}. This is important because the estimations of roentgen equivalent dosage always allow for the factor of decay.

NORMAL TISSUES

The D.A.R. for *skin and fat* was in all cases less than one. For fat it ranged from 0.1 to 0.2. For skin it ranged from 0.2 to 0.5. The D.A.R. for *muscle* varied from 0.2 to 1.9.

THERAPEUTIC CONSIDERATIONS

Treatment with radioactive phosphorus would be simply another form of radiation therapy. Its single significant difference from x-ray or radium therapy would be that it is administered orally or parenterally and distributed throughout the whole body, and the sources of the radiation are all within the tissues where the material is present. Therapy with radioactive phosphorus would be, therefore, systemic irradiation. Its localization in any tissue is, so far as is known, purely a metabolic phenomenon and takes place in accordance with the metabolic needs of the various tissues for phosphorus. Hence, in the treatment of any malignant neoplasm, its effectiveness will depend on its distribution within the body. If it should prove to be more effective than conventional radiation therapy, it will be so because of this, and especially if there is a favorable differential absorption by scattered tumor cells.

It is not the purpose of this paper to present a method for the therapeutic administration of radioactive phosphorus in any of the malignant neoplastic diseases studied. This is discussed in detail elsewhere (5). It should be pointed out, however, that large amounts of the isotope may depress the blood count or seriously damage the hematopoietic system. Therefore, any attempt to treat any malignant neoplasms with P^{32} should be undertaken only after careful study of the bone marrow of the patient. During the course of the treatment hematopoiesis should be carefully followed by frequent blood counts and occasional marrow studies.

SUMMARY AND CONCLUSIONS

Tracer amounts of radioactive phosphorus, P^{32}, have been administered to patients with carcinoma of the breast, osteogenic sarcoma, and lymphosarcoma. The radioactivity of portions of the different tissues removed at operation have been measured, and a ratio established in each instance between the amount of the isotope measured per kilogram of tissue and the amount of P^{32} administered per kilogram of body weight. This ratio has been designated the "differential absorption ratio" (D.A.R.), and has been used to compare the amount absorbed by the different tissues both in the same patient and in different patients, and to determine the maximum amount of radiation that might be delivered to a tissue if a therapeutic amount of the isotope were administered. It was found that radioactive phosphorus may be a very useful therapeutic agent in lymphosarcoma; that the isotope may be of value as a therapeutic adjunct in the treatment of osteogenic sarcoma and carcinoma of the breast.

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DISCUSSION OF PAPERS BY ZAHL AND COOPER AND BY KENNEY, MARINELLI, AND WOODARD

Paul S. Henshaw, Ph.D. (Bethesda, Md.): The papers by Dr. Kenney and Dr. Zahl are without doubt outstanding new contributions. These investigators bring to this meeting data carefully obtained on a pertinent subject, one in regard to which a real desire for information has existed.

Almost from the time artificially induced radioactive substances were first made available, the question has been discussed as to whether such substances might be introduced into patients in such a manner as to treat malignant disease effectively. Some attempt has been made by Lawrence and others to use radioactive materials in this way, but little is known as to whether it might reasonably be expected that enough radioactivity would reach the tumor area with this method to bring about a favorable reaction.

Dr. Kenney has gone straight to the bottom of the problem. He has selected one of the elements of the normal diet, phosphorus, rendered it radioactive, administered it to patients by way of the diet, and then examined such tissues as he could to determine the relative amounts of radiophosphorus present.

The study in its simplest terms was an investigation of phosphorus distribution. As it turned out, Dr. Kenney found an unequal distribution to various tissues and organs and—what is most important—an appreciably higher concentration in malignant tissues in certain cases.

More than this, Dr. Kenney made his measurements in such a way that he could get some idea of whether an adequate amount of radioactivity was reaching the malignant tissues. In this respect, also, his results are most encouraging, for they tend to show that for two of the three types of tumor investigated, close to an effective dose of radiation may be administered by this method.

Dr. Kenney's investigation has quite naturally been limited in its scope. One cannot but wonder about the distribution of radiophosphorus to tissues and organs not mentioned and also about the relative radiosensitivity of the various tissues subjected to radiation.

Dr. Kenney has pointed out that the limiting factors with radioactive phosphorus therapy are similar to those of conventional irradiation therapy—progressive anemia and leukopenia being among the more important destructive changes. This is a point which raises some apprehension. Although it may be found that blood-forming organs may retain a relatively smaller amount of radiophosphorus, is not the greater radiosensitivity of these organs likely to prove a real source of danger?

The one question I should like to ask Dr. Kenney is whether he has any information as yet about the relative amounts of radiophosphorus stored by the bone marrow, spleen, liver, etc.

Dr. Zahl's study begins where Dr. Kenney's leaves off. His attempt has been to find a substance which can be rendered radioactive and which, at the same time, is selectively absorbed by tumor tissues. Finding a substance that is absorbed in tumor tissues in appreciably greater amounts has been the ambition of many investigators and at last it seems that some success is being attained in this work. This development, added to that of Dr. Kenney, leads us to expect that some really worthwhile advances in the efficiency of radiotherapy lie just ahead.

Rollin Howard Stevens, M.D. (Detroit, Mich.): I wonder if Dr. Zahl will explain about the absorption of the neutrons in the lithium causing an immediate explosion. Is that a single sudden radioactive phenomenon? I understood him to say it was not radioactivity. Does that mean a comparatively large amount of energy delivered all at once to the cell containing the lithium? Is it comparable to a heavy single dose of radiation or to a constantly repeated small dose such as takes place when radium phosphorus is retained in the system and is active over a long period of time.

In regard to Dr. Kenney's paper, the question was asked, is there any damage done to the bone marrow? I believe he stated that the irradiation might go on for 100 days. I should like to ask if this is so.

I am unable to understand how, when the half-value period of radiophosphorus is something like fourteen and a half days, its activity is going on for 100 days. As I understand it, radium, for instance, taken internally, is largely excreted from the bone marrow within thirty days and the remainder is deposited in the trabeculae and cortex of the bone marrow. Many years ago I injected radium chloride intravenously in patients afflicted with leukemia and Hodgkin's disease, and a clear case of radium poisoning has recently appeared in a patient thus treated, after sixteen and a half years. Frequent examinations of the blood show no change whatever. A recent examination by Robley Evans showed 11.5 micrograms of radium still in the body. That is about twice the lethal dose. Why, then, does it not destroy the bone marrow and influence the blood picture? Why, therefore, expect any destruction of bone marrow from a radium phosphorus in the comparatively short active period of the phosphorus?

T. Leucutia, M.D. (Detroit, Mich.): I should like to add one question to that of Dr. Stevens. In the case of the neutron traversing a certain tissue and exploding the boron or lithium atom, what happens to the hydrogen atom, which after all is the constant unit atom of the body?

Robert R. Newell, M.D. (San Francisco, Calif.): This, of course, is an entirely new development. We have new tools to work with, and everybody is

trying, in every way he can think of, to use these tools. The idea, as I understand it, is to get something that will reach the tumor selectively and produce radiation.

Let us suppose we could find any substance at all that would go selectively to the tumor; let us suppose this were an organic substance and that we could attach a toxic radical to it. We would then have ordinary chemotherapy. The problem here is to find something that will reach, selectively, the thing we wish to destroy.

The first half of the problem—to find something which will carry radioactivity selectively to the tumor—seems to me to be no simpler than it might be to find something which would carry *any poison* selectively to the tumor. Indeed, with *any poison* we have a very much wider range of possibility than if we are going to insist on radioactivity or radiation of any kind.

Do I understand correctly that radiophosphorus is concentrated in tumors because of the concentration of nuclei there? If so, then we need to consider how long are the paths of the beta rays that come from it. If they are long, then neighboring nuclei irradiate each other. If they are short, then the beta ray concentration within the nuclei is similar for the tumor and for non-tumor tissue. And the nuclei are the vulnerable spots. So unless each beta ray reaches several nuclei, one can expect no better effect than from x-ray treatment of the whole body.

Paul A. Zahl, Ph.D. (*closing*): My answer to Dr. Newell's first question would be that in simple chemotherapy a poison injected into the blood stream to kill the tumor (or anything else) would probably kill or impair normal tissue as well. The very thing we are trying to accomplish is to inject an innocuous material and, after it has been localized in the malignant area, to render it "poisonous" by the use of neutrons.

To answer Dr. Henshaw's question, the particular lithium dyes with which we have worked are relatively non-toxic as far as their physiological effects on the normal organism are concerned.

Chairman Newell: May I offer another objection? It seems to me that the dye sticks in the tumor much better than the lithium and that a place for the lithium should be found which isn't out on the ionizable corner.

Dr. Zahl: That is the very matter we are now working on—namely, to attach slow-neutron-capturing materials to the localizing dye molecule in such a way as to prevent them from being metabolized and excreted independently of the dye molecule. This matter is essentially one of pure chemistry, and its solution probably hinges on bonding dynamics.

Chairman Newell: How well would these slow neutrons diffuse in the middle of a thick part?

Dr. Zahl: I should like to answer another question first. When a slow neutron is captured by a lithium atom, the release of energy is explosive and occurs instantaneously in the form of an alpha particle and a proton. The alpha particle has a very dense ionization path, of about 10 mu, while the proton, although having a somewhat greater penetration path, does not ionize as densely as the alpha particle. The relative biological effectiveness of such energies as alpha particles, protons, electrons, gamma rays, etc., is not well understood, although there is some evidence which indicates that the greater the density of an ionization path the greater its biological effectiveness.

A second question concerned the effect of hydrogen, oxygen, sodium, potassium, phosphorus, etc., normally found in tissue, and the amount of energy which will be released from the interaction of these materials with slow neutrons as compared with the energy released by various concentrations of lithium in tissue. In one of my lantern slides I pointed out a base line from which all the curves emerged. This base line represents the calculated amount of energy released by the elements normally present in tissue, and the curves rising from the base line represent the additional energy which would be released if varying concentrations of lithium were present in the tissue. This additional energy release we would hope to see localized to the malignant area, and so we conceive of attaining a sufficient energy differential to impair the malignant tissue more than the surrounding normal tissue.

If we were to postulate an actual clinical case we should probably start with a beam of fast neutrons directed toward a malignant area containing known concentrations of lithium. The penetration of the beam would depend on the velocity of the neutrons, the raying geometry, the location and depth beneath the skin of the tissue under treatment. The velocity of the neutrons would be reduced to the "slow" status either by the use of paraffin filters or by the natural slowing action of body tissue. By calculation one would hope to determine the appropriate speed so that a maximal action between the lithium and slow neutrons would occur where tissue destruction was most desired.

John M. Kenney, M.D. (*closing*): In answer to Dr. Henshaw's question about other tissues, we have had only one case that has come to autopsy so that we could investigate that possibility. Our plans call for a much wider study in that field. In our one autopsy, 103 days after the administration of the phosphorus, we found something in the order of 2 per cent of the administered dose in the liver, spleen, and kidneys particularly.

At the same time, the amounts that we measured were extremely minute, something on the order of one-hundredth to one-thousandth of a microcurie. We weren't measuring large quantities of radiation, but just enough to detect it and give us our measurements. While there was irradiation still going on,

the amount that was being administered was infinitesimal. The effective radiation that is administered by the radioactive phosphorus is practically all given within the first four weeks. After the fourth week whatever remains in the tissues, unless one gets an extremely high concentration, which we do not intend to do, will not be administering effective radiation.

With regard to dangers to the blood-forming organs, we have started some therapy along the lines suggested by this preliminary work. We find the bone marrow concentration, as I recall, to be roughly twice that of blood. We don't know even now what that is going to mean. We have seen a few changes, which the hematologists haven't been able to understand. There has been no increase in the erythroblasts or myelocytic elements, even though we have used doses as high as 12 millicuries in some of our patients. The change we see in our patients is not the type of change seen in the leukemias treated with this material, even with larger doses than we have used here.

As for the length of the beta ray path, it is approximately 4 mm. The effect is reasonably well localized. There will be some spread, but it will not exceed 4 mm., which is probably just about right.

The Absorption of Radiophosphorus in Irradiated and Non-Irradiated Mice[1]

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THE EXPERIMENTS to be described were undertaken primarily to investigate the effect of roentgen radiation on the gross phosphorus metabolism of some animal tissues. Albino mice of age greater than twelve months were used in three sets of experiments. Some were retained as controls; in the others, one leg was irradiated with 3,000 r (in air) of 190 kv. unfiltered x-rays, the exposure time being two minutes. The rest of the animal was covered with 1/8 inch lead sheet, which was sufficient to exclude all significant extraneous radiation. All animals were given tracer doses of P^{32} intraperitoneally in the form of Na_2HPO_4 solution and sacrificed at different times thereafter.[3] The irradiated groups IA, IIA, and IIIA were injected immediately after irradiation. Groups IA and IB were kept in metabolism cages with raised wire floors throughout the experiment, whereas the others were not. The essential data pertaining to the experiments are given in Table I.

TABLE I: OUTLINE OF EXPERIMENTS

Experiment and Group	No. and Sex of Animals	X-Ray Dose (r)	P^{32} Injected: Activity μcs.	P^{32} Injected: Volume (c.c.)	P^{32} Injected: Na_2HPO_4 (mg.)	Average Animal Weight (gm.)	Time Elapsed Between Injection and Sacrifice (days)	Animals Used in Each Determination	Tissues Assayed
IA	28F	3,000	5.21	0.5	0.9	29.0	0.9; 2.9; 6.9; 12; 19; 26; 33	4	Liver, spleen, kidney, bone, muscle, skin, blood, carcass
IB	28F	0	5.25	0.5	0.9	27.0	0.7; 3.7; 6.7; 11.7; 16.7; 23.7; 31.7	4	
IIA	28M	3,000	6.2	1.0	0.9	29.3	4; 9; 12; 16; 20; 28; 54	4	Muscle, bone, skin, liver, blood, carcass
IIB	8M	0	6.2	1.0	0.9	30.5	8; 11; 15; 20	2	
IIIA	28M	3,000	3.14	0.5	0.4	30.2	9; 10; 11; 12; 13; 14; 15	4	Muscle, bone, skin, liver, blood, carcass

Note: Diet common to all groups: Purina dog chow, lettuce, carrots, and water.

Dissection and weighing of the different tissues were performed immediately after sacrifice of the animals. The specimens were placed in metal jar caps about 3 inches in diameter, dried in an oven at 90° C., and ashed at about 500° C. in an electric furnace. Their radioactivity was compared to that of suitable uranium standards by means of a Geiger-Müller counter or a Lauritsen electroscope and corrected for radioactive decay to the time of injection. Suitable precautions were taken to avoid beta-ray absorption in the ash of the sample.

The procedure outlined above permits, to a certain degree, a study of both local and systemic effects of roentgen radiation on gross phosphorus metabolism. The

[1] Read before the Radiological Society of North America, at the Twenty-sixth Annual Meeting, Cleveland, Ohio, Dec. 2–6, 1940.

[2] Rockefeller Clinical Research Fellow.

[3] The radioactivity of the P^{32} administered was determined in The Crocker Radiation Laboratory of the University of California, to which the authors are indebted for the P^{32} used in these experiments.

local effects can be observed by a comparison between the P^{32} uptake in irradiated and non-irradiated tissues in the same animal, whereas the systemic effects can be observed by a comparison between non-irradiated organs and tissues in the irradiated animal and the same organs and tissues in the control animals.

LOCAL EFFECTS OF ROENTGEN RADIATION ON GROSS PHOSPHORUS METABOLISM

The tissues involved in this comparison were skin, muscles, and bone of the irradiated leg and the same tissues in the non-irradiated leg of the same animal. It is obvious that such a comparison on the same animal avoids variations due to systemic effects and makes possible the detection of relatively small differences which would otherwise go undetected. The data that follow provide ample proof for this statement.

No difference in P^{32} uptake per gram of weight was detected in irradiated muscle as compared to non-irradiated muscle. The average ratio of the first to the second, as ascertained in 21 determinations involving a total of 84 animals (Groups IA, IIA, IIIA), is 0.95 and the standard error of the mean is 0.05. No single determination was rejected in computing this figure or any of the ones that follow, and no trend was detected in the course of time up to fifty-four days after injection. In skin, also, no difference in uptake was detected within the limits of experimental error. The determination was made on 28 mice only (Group IA), and it was not repeated because it was soon realized that some radical improvements in technic would be necessary to ascertain any possible effect within narrower limits. The ratio of irradiated skin to non-irradiated skin was found to be 1.19 with a standard error of the mean of 0.26. The large experimental error is to be ascribed to many causes, such as the low P^{32} uptake of skin, the smallness of the specimen available, the possibility of external radioactive contamination by urine, the variable fat content of the skin, etc.

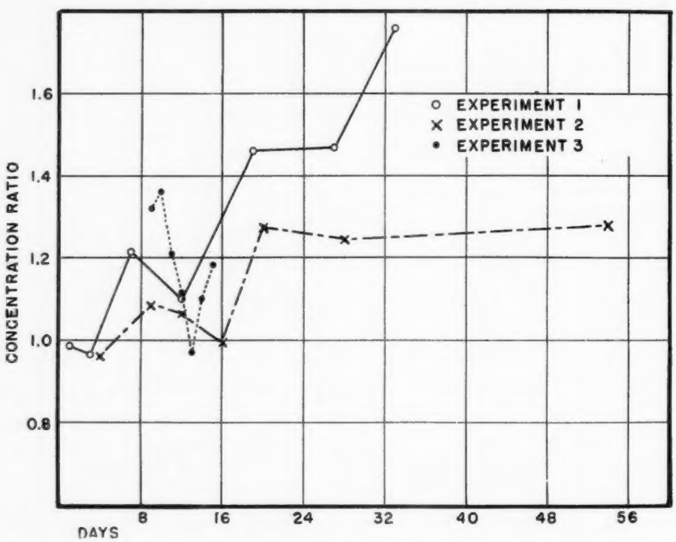


Fig. 1. The P^{32} concentration ratio of x-irradiated bone to non-irradiated bone in the same animal plotted as a function of time after administration.

The data on bone, on the other hand, show some significant differences in P^{32} concentration. In Figure 1 the ratio of P^{32} concentration in irradiated bone to P^{32} concentration in non-irradiated bone is

TABLE II: AVERAGE RATIO OF RELATIVE CONCENTRATIONS IN NON-IRRADIATED TISSUES OF IRRADIATED ANIMALS TO RELATIVE CONCENTRATIONS IN CONTROL ANIMALS

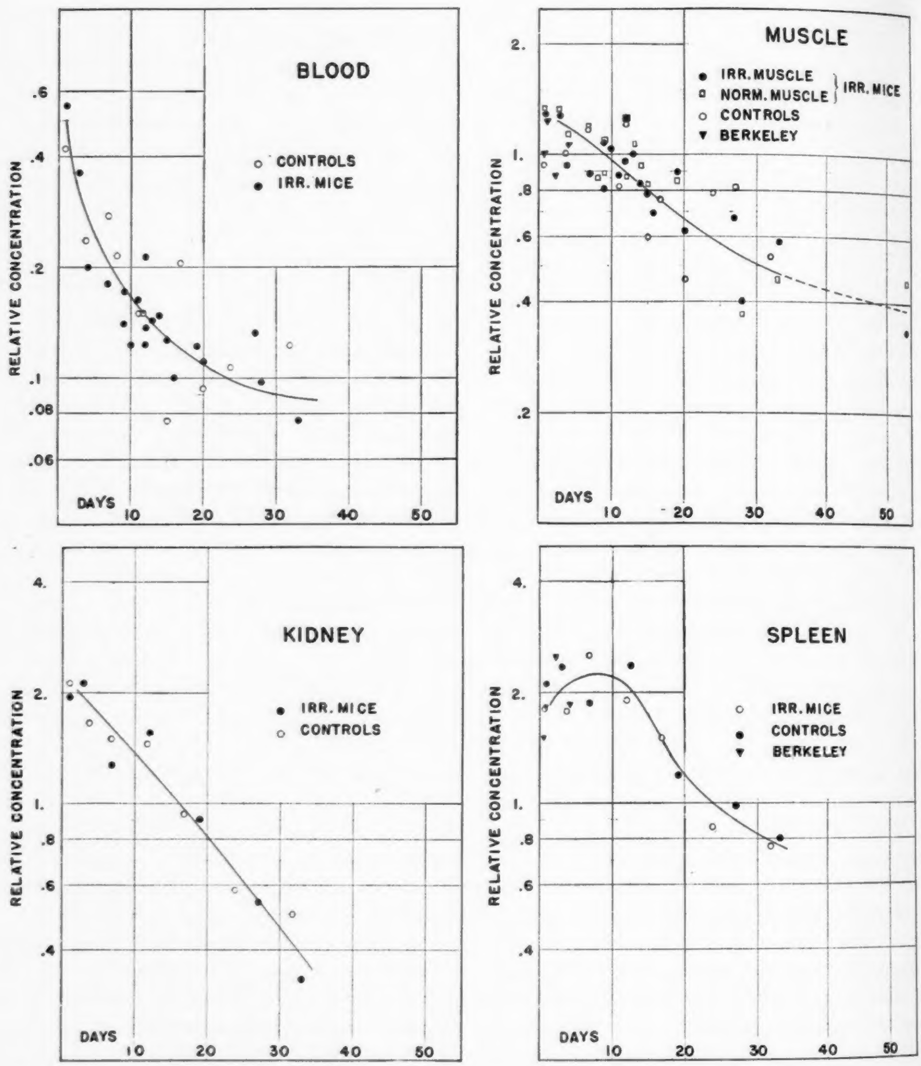
Tissue	Experiment	No. of Animals	Average Ratio	Standard Deviation	Standard Deviation of the Mean
Liver	I, II	92	0.95	0.37	0.11
Spleen	I	56	1.05	0.20	0.08
Kidney	I	56	0.94	0.19	0.07
Bone	I, II	92	1.18	0.41	0.12
Muscle	I, II	92	1.19	0.18	0.06
Blood	I, II	92	1.07	0.41	0.12

plotted, as a function of time after P^{32} injection, in three separate curves corresponding to the three experiments. The data as plotted show strong indication that, at least starting from the nineteenth day after injection, the P^{32} concentration of the irradiated bone is higher than the P^{32} concentration of non-irradiated bone. For this period of time the average ratio of the first to the second is 1.41, with a standard error of the mean of 0.07, the average being taken with 24 animals. The trend of the curves of Figure 1 indicates that a dip occurs in the concentration ratio somewhere between twelve and sixteen days after injection. It is difficult to attach definite significance to this observation, even though Experiments II and III were actually planned to confirm or disprove the twelfth day dip occurring in the curve of Experiment I. The dip was again observed on the sixteenth day in Experiment II and on the thirteenth day in Experiment III. The reluctance on the part of the authors to accept this variation as true is based primarily on the fact that the average ratio between the weight of the irradiated bones to non-irradiated bones between the twelfth and sixteenth days was found to be 1.14 ± 0.04, whereas the average weight ratio was only 1.03 ± 0.03 for the whole experiment. It is not possible now to determine whether this difference in weight was merely a coincidence of errors or was, instead, also a true radiation effect. It is realized also that no clear light is thrown by these results upon the action of radiation on bone, since they could easily be ascribed either to impaired metabolism on the part of the irradiated bone or to a repair process in the same. It is felt that no satisfactory explanation of the whole behavior is possible without further investigation, and that crucial experiments involving the injection of P^{32} at different times after irradiation are indicated.

SYSTEMIC EFFECTS OF ROENTGEN RADIATION ON GROSS PHOSPHORUS METABOLISM

As already mentioned, this type of effect was studied by comparing the P^{32} concentration of several non-irradiated tissues in mice treated by roentgen radiation on one leg, with the P^{32} concentration of the same tissues in the mouse groups retained as controls. In order to eliminate from the comparison, as far as possible, the errors arising from variations in P^{32} dosage and in excretion, as well as the influence of animal weight, the actual P^{32} concentration of any tissue was divided by the P^{32} concentration of the whole animal from which the tissue in question was removed. This ratio, which will henceforth be called the *relative concentration*, has been plotted for a number of tissues as a function of time elapsed after injection, and is shown in Figures 2–7. Some of the data from Berkeley (1) are included for comparison.

Analysis of the results indicates no significant differences between the control groups and the irradiated groups. The ratios of relative concentrations between the non-irradiated tissues in the irradiated animals and the same tissues in the corresponding control groups are tabulated in Table II. It is to be noted that the ratios in the 4th column of this table are the averages of ratios arising at different periods of time; therefore, the standard deviations and the standard errors of the mean shown in the adjacent columns of the table, although calculated according to statistical practice, assume a definite meaning only if the ratio in relative concentration is independent of time. That this is the case can be established by close inspec-



Figs. 2–5. The relative P^{32} concentration in several tissues of partially x-irradiated mice and control mice at different times after administration of the isotope. See also Figs. 6 and 7. Ordinates equal the ratio

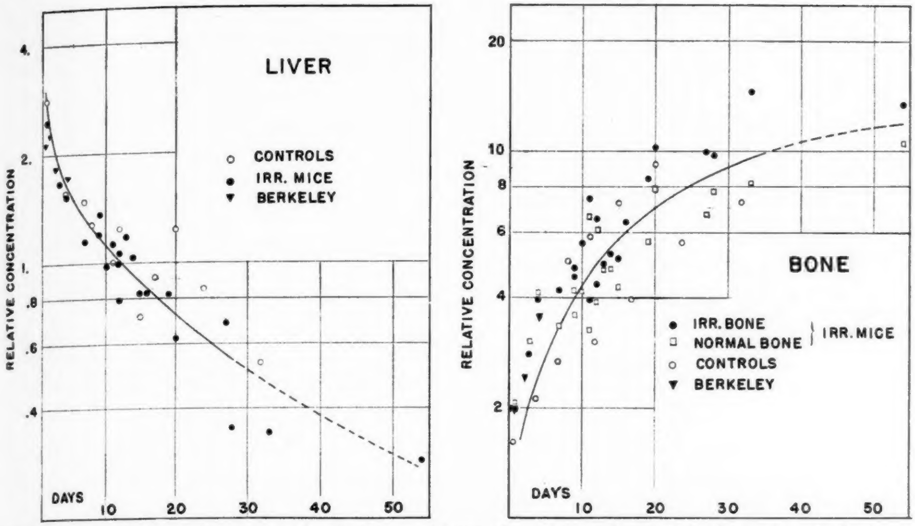
$$\frac{\text{concentration in tissue}}{\text{average total animal concentration}}.$$

tion of the data plotted in the above mentioned figures.

RADIATION DOSAGE DUE TO P^{32}

It has been shown that the radiation administered to a tissue by means of radioactive isotopes can be expressed in equivalent roentgens if the concentration of the substance in that tissue is known as a function of time (2, 3). The isotope concentration, in turn, depends on both radioactive disintegration and elimination of the isotope by the tissue.

From the material accumulated in these



Figs. 6–7. The relative P^{32} concentration in liver and bone of partially x-irradiated mice and control mice at different times after administration of the isotope. Ordinates equal the ratio

$$\frac{\text{concentration in tissue}}{\text{average total animal concentration}}$$

Note: The local effect on bone described before is masked by experimental variations in different animal groups but it is definite for all sets of animals sacrificed from the 19th day on.

experiments it is possible to evaluate the relative radiation dosage administered to the different tissues by the beta rays of P^{32}. It is necessary only to correct the P^{32} concentration of any one tissue for decay from the time of measurement to the time the animal was sacrificed in order to obtain the data necessary for the calculation. The same results, however, can be obtained from the data as already presented in Figures 2–7, once the average retention curve for the whole animal is calculated. This has been done in Figure 8. The ordinates represent the P^{32} present in the whole animal on different days after administration, expressed as a percentage of the administered P^{32}. They have been corrected for decay to the date of injection for the sole purpose of indicating the influence of metabolic elimination.

As is to be expected from the analysis of the preceding section, the P^{32} retention does not depend on partial roentgen irradiation of the animal. By dividing the per cent retention for each date by the average weight of the animal, the average concentration per gram of body weight, expressed in per cent of the dose given, is obtained as a function of time. This value, in turn, multiplied by the average relative concentrations shown in the foregoing figures, will yield the average concentration in the different tissues, expressed in the same terms. A plot of these values (corrected for radioactive decay to the date of sacrifice) will yield curves, the areas under which are proportional to the radiation doses received by the different tissues within definite time intervals. The curves seen in Figure 9 show the accumulation of radiation dosage with time. The doses are expressed in percentage of what may be called the administered total animal dose. This administered dose was based on the average total body concentration obtained by dividing the amount of P^{32} given by the weight of the animal, neglecting elimination.

It is seen that the animal as a whole receives only 22 per cent of this theoretical amount, that blood receives only 7 per cent and so on, but that bone receives in the

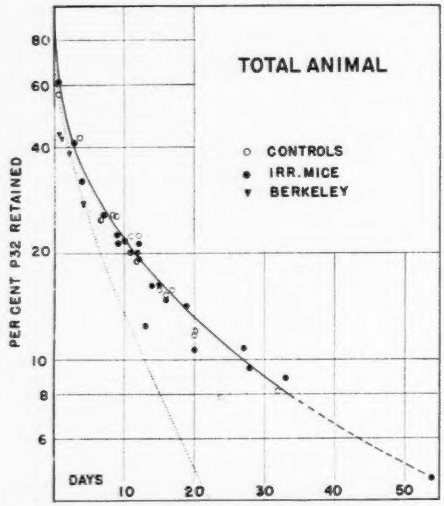


Fig. 8. The per cent retention of P^{32} in mice sacrificed at various times after administration. The solid line represents the P^{32} that would have remained in the animals had no radioactive decay taken place. The dotted line represents the actual activity of the animal on the day of dissection.

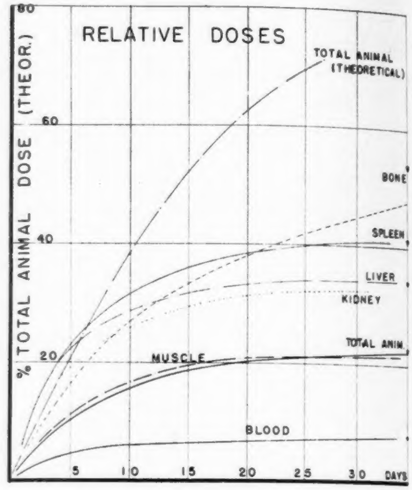


Fig. 9. The radiation dosage due to the beta-ray activity of P^{32} in different tissues. The ordinates represent per cent of administered total animal dose.

end up to 53 per cent.[4] It is worthy of notice that the relative doses accumulated at different periods of time differ, and that the ultimate total doses are reached practically within three weeks. It is recognized that, due to the small dimensions of certain organs in mice, the doses thus calculated are to be corrected because of the relatively long range of the beta particles from P^{32}. These particles tend to create "transition zones" along the boundaries of tissues having different concentrations. In these zones the ionization per unit mass varies from the average ionization in one tissue to the average ionization of the other. It is obvious that in some tissues or anatomical sites these transition zones may represent a great portion of a given tissue or may even overlap it; in these cases considerable corrections are needed for an adequate estimate of the radiation dose. The data, nevertheless, are here presented uncorrected because they are indicative of the distributions in specific ionization obtained with P^{32} when elimination of the isotope by the tissues is taken into account.

[4] It should be noted that the total radiation dose delivered by the P^{32} to the bone is very small in comparison to that delivered by the x-rays, actually not more than 90 equivalent roentgens in these experiments.

SUMMARY

The effect of x-ray radiation on gross phosphorus uptake has been studied by irradiating 84 mice on one leg, and by administering, immediately thereafter, P^{32} intraperitoneally. Thirty-six mice retained as controls were given P^{32} at the same time. Members of both groups were sacrificed at varying times afterward and the P^{32} content of various tissues was assayed.

Comparison between P^{32} uptake in muscle, bone, and skin of the irradiated leg and the P^{32} uptake in the same tissues of the non-irradiated leg of the same animal showed a greater P^{32} content in the irradiated bone. No significant difference was found in muscle and skin.

Comparison between several non-irradiated tissues in the irradiated animals and the same tissues in the control group failed to show any significant difference in P^{32} uptake.

The relative radiation dosages delivered

by P^{32} to several tissues assayed were computed by determining the concentration of the isotope in these tissues as a function of time. It was found that the rate of elimination of the isotope by a tissue is an important factor in the radiation dose actually received by such tissue.

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The authors wish to thank Dr. Failla for having suggested this experiment, and Miss A. Anschuetz for very able technical assistance during the course of the work.

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Elimination of Radioactive Elements by Patients and Rabbits after Injection of Thorotrast[1]

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Since thorotrast has been found useful as a contrast medium, it is of considerable interest to find out how thorium and its products are distributed in the body and to what extent these radioactive elements are eliminated. The danger from the continued exposure of the tissues to the emitted alpha, beta, and gamma rays makes such information still more important.

It is well known that thorotrast is absorbed rapidly by the reticulo-endothelial system and deposited for the most part in the liver and spleen. Previous studies by other investigators have contributed much information and have proved that the thorium remains long in these tissues. Pohle and Ritchie (1) report that the roentgen ray shadows cast by livers of rabbits, in which thorotrast was deposited, decreased slightly after considerable periods of time. Rigler (2) states that in man there is a noticeable decrease in the density of livers containing thorotrast after intervals of several years. This may be due to a redistribution of the thorium, as neighboring lymph nodes during the same period increase in density. Reeves and Morgan (3) have shown, by means of Geiger-Müller counter methods, a probable gradual decrease of the thorium content of the reticulo-endothelial system noticeable only over a period of years. Leipert (4, 5) found at autopsy about 60 per cent of the thorium in the liver and spleen of two patients who died a few days after injection. He found 97 per cent in the same organs at autopsy of a patient who had a bile duct block and died about sixty days after the injection of thorotrast. Jacobson and Rosenbaum (6) found 27 per cent thorium dioxide present in the ashed liver of a patient injected with thorotrast five years previous to death. At this hospital we have measured the gamma-ray activity from living patients by means of a Geiger-Müller counter, six or seven years after the injection of thorotrast. We obtained counts from the region of liver and spleen corresponding to about 20 per cent of the activity of the injected material. Wichmann and Fricke (7) examined the urine, by chemical and electroscopic means, of a patient who had been given thorotrast, without finding any trace of thorium or radioactivity. Leipert (4) investigated the blood, urine, and feces of dogs after thorotrast had been injected. No trace of thorium was found.

Leipert carried out a number of experiments with rabbits and determined the distribution of the thorium dioxide in different organs after different time intervals. From 58 to 75 per cent of the amount injected was recovered in the liver and spleen. The first animal was killed one day after injection and the last one 477 days after injection. The fluctuations in amount found showed no correlation with the elapsed time. Some thorium dioxide was also recovered from bone marrow, kidneys, and lungs. Per gram of tissue the liver and bone marrow contained about the same amount and the spleen about ten times as much. The amounts in the lungs decreased with time. The organs of five patients who died two, four, forty-two, forty-eight, and sixty days after intravenous injection of thorotrast were also examined, with somewhat similar results. The main difference was that the amount of thorium dioxide per gram of spleen in these human subjects was no higher than in the liver. Too little bone marrow was examined.

[1] Aid for this investigation was received from the research funds of the Graduate School of the University of Minnesota. The paper was presented before the Radiological Society of North America at the Twenty-seventh Annual Meeting, Cleveland, Ohio, Dec. 2–6, 1940.

TABLE I: RADIOACTIVE ELEMENTS PRODUCED BY THORIUM

Name	Main Isotope	Half-Value Period	Rays	Equilibrium Relative Amount	Range of α-rays
Thorium	Th	1.3×10^{10} years	α	10^{15}	2.6 cm.
Mesothorium I	Ra	6.7 years	β	10^{6}	...
Mesothorium II	Ac	6.1 hours	β, γ	10^{2}	...
Radiothorium	Th	2.0 years	α	10^{5}	3.7 cm.
Thorium X	Ra	*3.64 days*	α	10^{3}	4.1 cm.
Thoron	Rn	54 seconds	α	0.2	4.7 cm.
Thorium A	Po	0.14 second	α	10^{-3}	5.4 cm.
Thorium B	Pb	*10.6 hours*	β, γ	10^{2}	...
Thorium C	Bi	1 hour	α, β, γ	10	8.2 cm.
Thorium D	Pb	Stable	..	..	...

Before describing our studies it is necessary to call attention to the fact that a series of radioactive elements are produced continuously from the thorium. These elements and some of their important characteristics are given in Table I (9). Considering the small amounts of any of these elements that could possibly be present outside of thorium, it is evident that only thorium itself can be found and identified by chemical analysis. Appreciable damage to cells from radiation may, however, be produced by all elements emitting alpha rays. It is therefore of importance to determine the distribution of the different elements by means of radioactive methods.

Tissues, blood, feces, and urine collected for examination were ashed. A thin layer of the respective ash was spread on a filter paper which fitted into a cylindrical metal box used as an ionization chamber. This box was 18 cm. in diameter and 26 cm. in height. It was placed on top of a Wulff bifilar electrometer. A central copper wire 21 cm. long was attached to the electrometer lead and extended along the axis of the chamber. The ionization measured by means of the electrometer was practically all due to alpha rays. Preliminary measurements were made with small amounts of thorotrast mixed with 4 gm. of ashes. In this manner 0.005 c.c. of thorotrast could be detected (Fig. 1).

The first investigation was made to determine the elimination of radioactive elements by patients with old deposits of thorium in liver and spleen (10). Two patients who had received intravenous injections of 75 c.c. of thorotrast six and seven years previously returned to the hospital for a check-up. Several samples of feces were

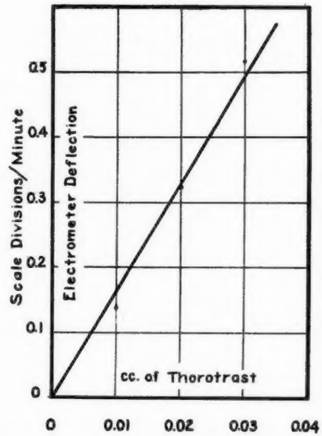

Fig. 1. Electrometric determination of thorotrast mixed with ashes.

collected and ashed. The radioactivity of the ash was determined as a function of time. The original activity of one such sample was equal to the activity of 0.1 c.c. of thorotrast. It decreased, however, with time to one-half, in about one hundred hours. As can be seen in Table I, thorium X has a half-value period of 3.64 days or 87.4 hours. Since no other element in the thorium series has a half-value period anywhere near this, it seemed evident that the radioactivity in the feces was attributable mainly to thorium X and, probably, a small amount of long-period elements.

The discharge of the electrometer expressed in scale divisions per minute was

plotted on a semilogarithmic scale against the time measured in hours, as shown by the dots in Fig. 2. The lower curve (A) shows the decrease of radioactivity with time for thorium X in equilibrium with its disintegration products, as calculated from the known disintegration constants. Curve B shows the decay of a mixture of 95 per cent thorium X and 5 per cent of a preceding long-lived product of the thorium series (thorium, mesothorium I or radiothorium), while curve C illustrates a mixture of 91 per cent thorium X and 9 per cent of the long-lived element. The initial radioactivity has been made the same in all cases and adjusted to fit best the experimental points. Curve B comes closest to the points, and the radioactive elements present in the feces in this case seem to consist of approximately 95 per cent of thorium X and 5 per cent of a long-period element, each in equilibrium with its disintegration products. The difference in the range of the alpha particles has not been taken into consideration in this calculation.

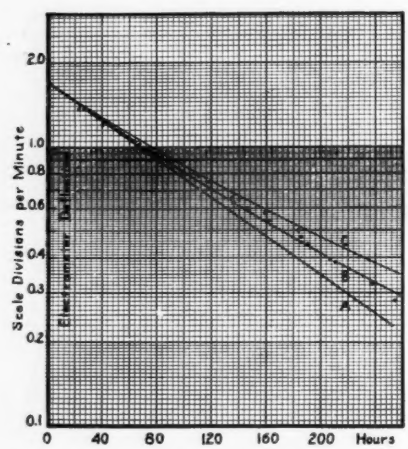

Fig. 2. Determination of radioactivity in ashed feces. See text.

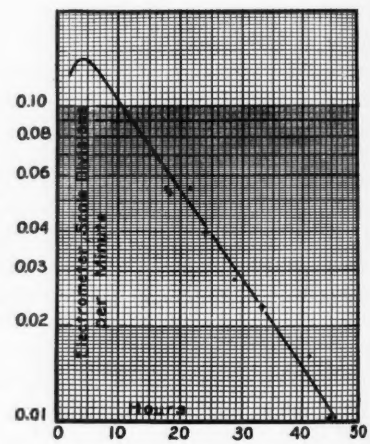

Fig. 3. Determination of radioactivity in the breath. See text.

Measurements four months later, when the thorium X had practically disappeared, indicated that only 2 to 3 per cent of the activity was due to elements with long periods. Other samples of feces from the two patients gave similar results. Several samples of ashed feces from persons who had never had any thorotrast injected were also examined but in no instance was any radioactivity discovered.

The patients did not stay long enough in the hospital for more complete studies. Some samples of urine were obtained, but it was more difficult to discover radioactivity in these, possibly due to the heavy ash. Unfortunately the urine was not examined quickly enough, but in one sample from the second patient slight radioactivity was noticed, which decayed with time. One sample of sputum was collected over twenty-four hours and when ashed failed to show any measurable radioactivity.

As the gas, thoron, is formed from thorium X, it seemed advisable to examine the breath of the patients, even though the half period of thoron is only fifty-five seconds. For a period of one to two hours the patient exhaled through a rubber tube into a closed cylindrical metal container of 30 cm. diameter and 30 cm. height. Several small holes in the cover provided for the escape of the exhaust air. A copper wire with an active length of 21 cm. extended along the axis of the container. Insulated from the grounded con-

tainer and kept at a negative potential of about 2,000 volts, it served to collect the radioactive deposit caused by the disintegration of the thoron. After the collection had been made, the wire was transferred and used as the central electrode of the ionization chamber on top of the electrometer. As thorium A has a half period of only 0.14 second, the deposit on the wire would consist mainly of thorium B with a half period of 10.6 hours. The alpha rays would come from thorium C, which has a half period of about one hour. A reasonable amount should be deposited in one hour, but the activity would continue to increase for a relatively long time and would be considerably greater if the patient were breathing into the container for twenty to thirty hours.

Figure 3 shows the result of a typical experiment plotted as in Fig. 2. The curve shows the expected change in activity as calculated from the known disintegration constants. During the first few hours there is an increase until equilibrium has been reached between thorium B and C. Then the activity falls off as thorium B disappears. Though the intensity is low, it is evident that the measured values, represented by the dots, agree with the predicted values within the experimental error. This proves that thorium B was deposited on the wire and that thoron, therefore, must have been exhaled by the patient.

If it is assumed that radiothorium is in equilibrium with thorium in the tissues, then it is possible to estimate the amount of thorium X produced per day and the proportion of this amount which is excreted. According to such calculation, it would seem that between 1 and 10 per cent of thorium X is excreted. Mesothorium I and thorium X are both isotopes of radium and it could therefore be expected that mesothorium I would be excreted to a similar extent. It is difficult to determine directly the excretion of this element due to the fact that it does not emit alpha rays. By saving the ash and remeasuring its activity after a couple of years more information should be obtained, as radiothorium would gradually be formed if mesothorium were present and the alpha ray activity would therefore increase over a period of years. Measurements taken after one year showed only a slight increase in activity over those taken four months after collection, but the intensity was so small that the experimental error was large. The amount of mesothorium must have been small in this sample. Possibly most of it had already been excreted. Gamma ray measurements with a Geiger-Müller counter placed over the liver of the patient gave a value corresponding to about 15 c.c. of thorotrast. The elements emitting gamma rays are mesothorium II, thorium B, and thorium C. It is impossible at the present time to estimate the relative amount of the different elements remaining in the tissues. It is evident, however, that the amount of thorium is greater than estimated fr m gamma ray measurements. The elimination of thorium X, thoron, and possibly mesothorium I, is of importance as it reduces the alpha ray activity in the tissues.

In order to obtain more information concerning the distribution of the different radioactive elements in tissues and the excretion of these elements, experiments were carried out with three rabbits. I am obliged to Mr. Jun-ch'uan Wang for this work. The experimental procedure was as follows:

1. Rabbit was weighed and placed in special cage with floor separating feces and urine.
2. One day's collection of feces and urine was ashed[2] and used as control.
3. Colloidal thorotrast, 2 c.c., was injected through vein in one ear.
4. Radiograph of abdominal and thoracic regions was made one hour later.
5. Five c.c. of blood was withdrawn from the other ear five hours after injection, ashed, and tested for presence of radioactivity.
6. Daily collections of urine and feces were made except over week-ends.
7. The first measurement of each was made about twenty-four hours after the collection

[2] The collections were weighed, dried in oven, burned, nitrated with HNO_3 burned again, and the ashes weighed.

TABLE II: RADIOACTIVITY OF ASH FROM FECES AND URINE OF RABBIT NO. 2, COMPARED TO CUBIC MILLIMETERS OF THOROTRAST

Days after Injection of Thorotrast	Feces (c.mm.)	Urine (c.mm.)	Total (c.mm.)	Total/-Day (c.mm.)
1	15.0	15.0	30.0	30.00
3	16.5	5.6	22.1	11.05
5	26.0	6.6	32.6	16.30
7	16.6	7.2	23.8	11.90
9	14.6	4.2	18.8	9.40
12	25.4	..	25.4	8.13
16	86.0	4.7	90.7	22.68
20	20.2	6.1	26.3	6.58
22	9.4	..	9.4	4.70
26	10.3	4.7	15.0	3.75
28	13.2	4.7	17.9	8 95
30	9.8	8.0	17.8	8.90
34	4.2	4.7	8.9	2.22
36	14.5	3.8	18.3	9.15
40	19.7	22.2	41.9	10.48
42	14.1	7.1	21.2	10.60
44	10.3	5.2	15.5	7.75
47	5.6	6.1	11.7	3.90
49	8.6	9.0	17.6	8.80
53	8.5	9.8	18.3	4.58
57	5.6	5.2	10.8	2.70
61	16.0	4.7	20.7	5.18
63	10.8	4.7	15.5	7.75
67	25.8	9.2	35.0	8.75
69	10.3	7.5	17.8	8.90
71	9.4	6.8	16.2	7.60
75	16.7	6.1	22.8	4.70
105	6.1	5.2	11.3	5.65

was made. Follow-up measurements were made for each specimen for various intervals of time to determine its rate of radioactive decay.

8. Rabbit was anesthetized and as much blood as possible was withdrawn before the animal died. The following organs were removed[3]: (1) liver, (2) spleen, (3) marrow of the two tibias and the two femurs, (4) shafts of these bones, (5) blood (75 c.c.), (6) lymph nodes, (7) brain, and (8) gallbladder. The activities of these organs were measured from time to time to observe changes in activity.

All three animals had running stools with blood clots and mucus the fifth or sixth day after the injection. This condition continued in one rabbit until it died after five days. The other two animals recovered and the stool became normal after four days.

Sixty-four samples each of feces and urine were collected. All showed a fair amount of activity, which decreased with

[3] The collections were weighed, dried in oven, burned, nitrated with HNO_3 burned again, and the ashes weighed.

TABLE III: RADIOACTIVITY OF ASH FROM FECES AND URINE FROM RABBIT NO. 3, COMPARED TO CUBIC MILLIMETERS OF THOROTRAST

Days after Injection of Thorotrast	Feces (c.mm.)	Urine (c.mm.)	Total (c.mm.)	Total/-Day (c.mm.)
1	11.6	20.0	31.6	31.6
2	6.1	19.5	25.6	25.6
3	13.7	9.8	23.5	23.5
4	25.8	14.1	39.9	39.9
7	21.8	10.5	32.3	10.8
8	12.6	7.5	20.1	20.1
9	10.8	8.7	19.5	19.5
10	13.6	10.5	24.1	24.1
11	16.4	11.3	27.7	27.7
14	22.6	6.1	28.7	9.6
15	8.6	16.4	25.0	25.0
16	8.9	10.8	19.7	19.7
17	15.0	2.2	17.2	17.2
18	10.3	..	10.3	10.3
21	9.8	9.4	19.2	6.4
23	8.9	8.5	17.4	17.4
24	15.0	10.1	25.1	25.1
25	15.7	12.2	27.9	27.9
28	26.3	12.7	39.0	13.0
29	30.6	6.8	37.4	37.4
30	28.5	13.2	41.7	41.7
31	14.1	8.9	23.0	23.0
32	15.7	7.5	23.2	23.2
35	14.5	9.8	24.3	8.1
36	13.7	..	13.7	13.7
37	19.3	12.2	31.5	31.5
38	16.9	8.9	25.8	25.8
39	6.1	..	6.1	6.1
42	24.4	17.8	42.2	14.1
43	21.6	5.6	27.2	27.2
44	15.0	3.3	18.3	18.3
51	16.9	3.8	20.7	20.7

time. The rate of decay varied to a certain extent but was in all cases close to that of thorium X. It was evident, therefore, that the activity in the urine and feces was due mainly to thorium X. The radioactivity was compared to that of thorotrast. Tables II and III show the amount of thorotrast in cubic millimeters with the same activity as the samples. From the measurements it is estimated that about 10 per cent of the thorium X formed in twenty-four hours is excreted.

Table IV gives the radioactivity of different organs of the rabbit which was killed 127 days after injection of thorotrast. The figures represent the amount of thorotrast in cubic centimeters which showed the same radioactivity as the samples. It is interesting to note that the activity in the ash from liver, spleen, and bone increased with time. This indicates that these organs contained long-period ele-

TABLE IV: ANALYSIS OF ACTIVITY IN DIFFERENT ORGANS

Organ	Weight		Activity			
	Fresh	Ash	1st Measurement Thorotrast Equivalent	2nd Measurement Thorotrast Equivalent	Interval of Days	Amount of Activity in Relation to Time
Liver	130.0 gm.	2.367 gm.	1.33 c.c.	1.64 c.c.	21	Increasing
Spleen	1.4 gm.	0.10 gm.	0.321 c.c.	0.333 c.c.	8	Increasing
Marrow	2.0 gm.	0.16 gm.	0.089 c.c.	0.1025 c.c.	14	Increasing
Shaft of bone	64.15 gm.	25.3 gm.	0.027 c.c.	0.031 c.c.	6	Increasing
Blood	77 c.c.	0.55 gm.	0.0015 c.c.	0.000 c.c.	25	Decreasing
Lymph nodes	5.2 gm.	0.095 gm.	0.0027 c.c.	0.0014 c.c.	7	Decreasing
Brain	9.8 gm.	0.419 gm.	0	0	..	....
Gallbladder	2.1 gm.	0.0513 gm.	0	0	..	....

ments and that the short-period elements were gradually increasing in amount—another proof that the latter had been partially removed from the organs in the living animal. The amount of radioactivity per gram of material was twenty times greater in the spleen than in the liver and four times greater in the bone marrow than in the liver. The shafts of the bones contained a very small amount. The radioactivity in the blood and in the lymph nodes was evidently due mainly to the presence of thorium X. The small samples of blood taken from the ear five hours after injection did not contain enough radioactive material to give reliable measurements. The thorium dioxide must have almost completely disappeared from the blood after this short interval.

SUMMARY

As far as the distribution of thorium in the tissues is concerned the values obtained in our experiments agree with reports of other authors. The main information this investigation adds is that some elements in the thorium series are distributed in a different manner and are eliminated to a considerable extent from the tissues. The presence of thorium in a living animal or patient can be revealed by means of gamma-ray measurements, but such measurements do not give quantitative values for the thorium. Thorium X is consistently found in the feces and thoron is exhaled in the breath. For quantitative determinations of the different radioactive elements in the thorium series it would be necessary to determine the range of the alpha particles and also to make beta-ray measurements. The relative amounts of the different elements depend to a certain extent upon the time elapsed since the thorium was concentrated.

Excretion of thorium after intravenous injection of thorotrast in patients has not been discovered as yet and these studies show that a great portion of the thorium must have still remained in the tissues of two patients who received injections six and seven years prior to the measurements.

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DISCUSSION

Robert Taft, M.D. (Charleston, South Carolina): Unquestionably the reason I was asked to say something about Dr. Stenstrom's paper is that it was I who probably first suggested that thorotrast might be dangerous to use. A good many years ago I demonstrated that simply from a physical standpoint the average dose of thorotrast, 75 c.c., gives equivalent gamma radiation of 1.3 micrograms of radium. I pointed out, furthermore, that 2 micrograms of radium in the body could produce death within ten years' time. These observations I called a preliminary report, hoping that I—or somebody else—would see how long this material remained in the tissues. I have not had the privilege of studying any patient over a number of years, as I never made these injections since I didn't approve of them. I was able, however, to borrow a few patients from Dr. Rudisill of Charleston, who had given these injections, in the Roper Hospital Clinic, in several cases. All these patients are now dead, not necessarily as a result of the thorotrast but because they were in rather desperate condition at the time the work was done. An autopsy was done on one and thorotrast was demonstrated in the tissues in a good many places. About 50 per cent of the original dose was found in the liver, some two or three months after injection.

A study of Dr. Stenstrom's paper throws a new light on this matter. He has assured us that with these decayed products of thorium a good deal will be eliminated over a period of time, for which reason the procedure would appear to be less dangerous than I originally feared. I do, however, very seriously doubt the value of thorotrast injections in man. From an experimental standpoint the work with rabbits is excellent, but I do not feel that the clinical findings warrant the injection of thorotrast into a patient. I do not believe it yields enough information to warrant the risk which is involved.

When I am asked what I now think of the injection of thorotrast, I invariably answer that I believe it may be given in any part of the human body where it will drain out.

Leo G. Rigler, M.D. (Minneapolis, Minnesota): We have injected thorotrast in about 275 patients over a period of years and have had opportunity to observe a reasonable number of these later on. We have just completed a study of 8 patients who received thorotrast injections somewhere between five and eight years ago, and the most careful study that we could make of liver function, spleen function, and bone marrow function, by all the usual tests, produced no evidence whatever that the thorotrast had done any harm in these particular patients. We didn't use quite as large a dose as Dr. Taft mentioned, but something approximating that.

We are very much afraid of thorotrast when it is introduced in certain portions of the body. We have seen the development, for instance, of fibroma or some type of foreign body tumor under the skin in two cases where the thorotrast, by error, failed to get into the blood stream and was enclosed in the tissues. We have also had the unfortunate experience of introducing thorotrast into the peritoneal cavity by accident when it was supposed to be injected into the common duct. In this instance the patient developed a very severe reaction which looked like a peritonitis. Fortunately it was temporary, but was alarming at the time.

We have hesitated to use thorotrast in the spinal canal, not because of its ultimate effects but rather because of the possible immediate effect upon these tissues.

This chapter, of course, is far from closed and will remain uncompleted for many years. We are using thorotrast very much less today than we did eight years ago, when we began, but I still have to find a patient furnishing adequate proof that any appreciable harm was done by the injection.

Wilhelm Stenstrom, Ph.D. (*closing*): I wish to thank Dr. Taft and Dr. Rigler for their discussion. I agree completely with Dr. Taft and still consider it very serious to inject thorium intravenously. We undertook it to see if by a very sensitive method we could find thorium excreted. So far we have not found any thorium, but we have found that some of the radioactive substances in the series are excreted and that the radiation, therefore, is not quite as great as if they were retained. There is still, of course, radioactivity in the tissues.

Further Studies on Effects of Irradiation on Proliferation and Metabolic Processes of Normal and Malignant Mammalian Tissues

V. Effects Produced by Different Dosage Rates of X-Radiation upon Growth Factors of Mouse Sarcoma 180 Grown in Vivo Following Irradiation in Vitro[1]

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A PREVIOUS communication (1) recorded effects produced by different dosage rates of x-radiation on the proliferation *in vitro* of various mammalian tissues, both normal and malignant. In the present series of experiments the attempt was made to evaluate the time intensity factor for given doses of filtered and unfiltered x-radiation in relation to their effect upon growth factors of mouse sarcoma 180 grown *in vivo* following irradiation *in vitro*.

MATERIAL AND EXPERIMENTAL PROCEDURE

Tiny fragments of mouse sarcoma 180 were used as test objects. The technic was that employed in the previous experiments (1) except that the tissue fragments were implanted subcutaneously in both axillae of each mouse instead of in a culture medium. Tumors about eight to ten days old were removed from the animals under strict aseptic precautions and cut into tiny fragments with very sharp scissors. Portions of the cut tumor fragments were spread on a round coverslip, No. 1 (22 mm. diameter), previously attached to a square mica sheet (the thickness of both being about 0.25 mm.), and were covered with a Maximow slide, sealed with paraffin wax, and irradiated. To avoid any evaporation of the tissue, a fragment of moist filter paper was placed in the concavity of the Maximow slide. Immediately after irradiation the tumor fragments were suspended in sterile saline solution. Portions of about 0.3 c.c. of the suspension were injected into each axilla of the mouse by means of a tuberculin syringe and an 18-gauge hypodermic needle. The inside diameter of the tip of the bore of the syringe was 0.57 mm. Hence the diameter of the implanted irradiated sarcoma fragments could not exceed 0.57 mm. The average thickness of six fragments was 0.7 mm. The weight of the fragments varied from 0.05 to 0.08 mg. The reason for using such small tissue fragments was to insure more uniform distribution of the absorbed radiation and the implantation of fairly equal portions of the irradiated tissue fragments in the different animals.

The time elapsing between the removal of the tumor from the animal and implantation of the irradiated tumor fragments in other animals was about one hour. Mice six weeks to two months old of the C.F.X. strain from Coward's Farm, New City, N. Y., were used in all experiments. In previous experiments these mice have given 100 per cent takes with very few spontaneous regressions. In the rare instances when 100 per cent of takes among animals did not occur, or when spontaneous regression ensued, the experiment was repeated. For each experiment 10 to 12 mice were used, with an equal number of controls. Implants were placed in both axillae, as these have proved to be favorable sites for tumor growth, which confirms the observations made by Sugiura (2); also double experimental data were thus provided. The experimental and control mice were kept

[1] From the Division of Cancer, Department of Hospitals, New York City, and the Department of Experimental Surgery, New York University Medical College. Read by title before the Radiological Society of North America, at the Twenty-sixth Annual Meeting, Cleveland, Ohio, Dec. 2–6, 1940.

under the same conditions, fed with dog chow and allowed water *ad libitum*.

In studying the effects of irradiation on living processes a number of factors must be taken into consideration. The following growth characteristics were chosen in evaluation of the results in the present investigation: (1) percentage of takes, (2) the latent period, (3) the average growth period of the tumors, (4) the first measurable tumor size following the latent period, (5) the maximum tumor size, in average diameter, (6) the percentage of regressions. The latent period is the time from implantation to the occurrence of a palpable, measurable tumor. Although, in some instances, palpable tumors could be observed five to six days following implantation, the first measurements were made, by means of vernier calipers, on the seventh or eighth day. After the seven to eight day period the percentage of takes, particularly among the control mice, could usually be judged with certainty and used as a basis for comparison with the latent period in the experimental mice. The increase in size of the proliferating tumors, starting from the first measurement, was followed every second day until the tumor either began to ulcerate or to regress. In case of tumor regression, the maximum size attained by the tumor was considered. Only the averages of the initial tumor sizes, *i.e.*, following the latent period, and the average sizes to which the tumors developed following the active period of proliferation in experimental mice as compared to the controls, were considered in evaluation of a given dose of x-radiation. The active proliferation period is the time from the first measurement of the tumor, following the latent period, to the time when ulceration or regression began. The measurements of the tumor taken were length and width, and the thickness when possible. For the sake of brevity only the average of two dimensions is recorded in the tables. The regression of tumors was considered complete when they had gradually disappeared without a trace of recurrence after one or two months.

EXPERIMENTS WITH FILTERED 200 KV. X-RAYS

Two dosage rates of filtered x-rays, 40 r/min. and 640 r/min. ±10 per cent, were used (±10 per cent representing the difference in rate in various experiments). The time ratio was in each instance 1:16. The source of x-rays for both dosage rates was a pulsating potential two-valve Waite generator with an oil-cooled Westinghouse oil-immersed x-ray tube having an inherent filtration equivalent to approximately 0.2 mm. Cu, the physical factors being 200 kv., 20 ma., 0.5 mm. Cu and 1 mm. Al filter, and a half-value layer of 0.85 mm. Cu. With a tissue-target distance of 12.5 cm. and 50.0 cm., the above mentioned dosage rates as measured in air without back-scatter were obtained by the use of a special small thimble-type ionization chamber calibrated against a standard guarded-field air-type ionization chamber. The field exposed to radiation was from 15 to 17 mm. in diameter. For each dosage rate an equal number of mice were inoculated in both axillae as described above. An equal number of mice were injected with unirradiated tumor fragments as controls. The period of two to three weeks following the latent period, *i.e.*, after the first measurements were made, was found to be the most appropriate for studying the growth characteristics of this type of tumor. After this period some of the tumors, particularly the fast-growing control tumors, began to ulcerate; on the other hand, some tumors which originated from irradiated fragments began to regress.

In Tables I and II are recorded the results obtained from effective doses of filtered x-rays using the two dosage rates, with a time ratio of 1:16. The data included in these tables are only an excerpt from the numerous observations made. Some effects were produced by smaller doses (800 to 1000 r) than indicated in the tables. These, however, were not particularly marked. More notable effects upon the growth characteristics of the tumor, such as the latent period, percent-

TABLE I: EFFECTS OF FILTERED 200 KV. X-RAYS UPON GROWTH FACTORS IN VIVO OF MOUSE SARCOMA 180
(Dosage rate 40 r/min. in air ±10%. Tissue-target distance 50.0 cm.)

Dose in r	Time of Irradiation	Av. Latent Period in Days	Takes (per cent)	Initial Tumor Size (cm.)	Av. Growth Period in Days	Max. Tumor Size, Av. Diameter (cm.)	Regressions (per cent)	Remarks
1,100	23′ 5″	9.0	85.0	0.4 × 0.3	29.0	1.9 × 1.0	25.0	First measurable tumors appeared 7 days, others 11 days after implantation
1,300	27′38″	10.8	84.5	0.4 × 0.3	20.0	1.5 × 0.9	32.5	First measurable tumors appeared 7 days, others 12 days after implantation
1,500	30′18″	11.0	80.0	0.3 × 0.2	13.2	1.4 × 0.8	44.4	First measurable tumors appeared 10 days, others 12 days after implantation
1,500	38′24″	12.0	72.8	0.4 × 0.4	19.0	1.1 × 0.5	50.0	First measurable tumors appeared 10 days, others 15 days after implantation
1,600	36′ 0″	12.8	50.0	0.4 × 0.4	18.0	0.9 × 0.6	50.0	First measurable tumors appeared 12 days after implantation, others later
1,800	40′32″	14.9	40.7	0.3 × 0.4	19.0	0.7 × 0.6	75.0	First measurable tumors appeared 14 days, others 16 days after implantation
1,800	41′ 0″	15.0	41.7	0.3 × 0.2	25.0	1.1 × 0.8	83.0	First measurable tumor appeared 11 days, others 16 days after implantation
1,900	43′36″	16.0	14.2	0.4 × 0.3	21.0	1.2 × 0.8	100.0	First measurable tumors appeared 12 days, others 14 days after implantation
2,000	45′ 0″	17.0	5.5	0.3 × 0.2	20.0	0.9 × 0.8	100.0	Only one tumor occurred 17 days after implantation but eventually disappeared
2,200	51′12″	0	0	0	0	0	0	

age of takes, etc., began to appear among animals injected with tumor fragments which had been irradiated with doses above 1,000 r.

Analyzing the data in Table I (low dosage rate), a constant increase can be noted in the latent period, a decrease in percentage of takes, and an increase in the percentage of regressed tumors, corresponding roughly to the increase in the dose. On comparing the sizes of the tumors (initial and maximum) no clear-cut relation to the dose of radiation can be seen. In some instances, tumors originating from sarcoma fragments irradiated with higher doses developed to larger sizes than those originating from tumor fragments previously irradiated with smaller doses. The same can be said of the initial tumor sizes following the latent period. This phenomenon may be explained by assuming that the portion of the irradiated fragment which was inoculated into one mouse contained more viable cells than the portion implanted into another mouse, resulting in tumors slightly different in size. Another point which should be brought out is the prolongation of the latent period. In the same experiment, for example, when an effective dose of irradiation was used, some measurable tumors appeared nine days and others not until fifteen days following implantation. This phenomenon may also be explained by assuming that only a few viable cells were implanted into a given mouse, requiring a longer period of time to produce a tumor of a palpable, measurable size, or it may be that the reproductive ability of these particular cells was more affected by the given dose of radiation, requiring a longer period of time for recovery. The average latent period, however, as indicated in the table, increased with the increase of the dose of radiation.

TABLE II: EFFECTS OF FILTERED 200 KV. X-RAYS UPON GROWTH FACTORS IN VIVO OF MOUSE SARCOMA 180
(Dosage rate 650 r/min. ±10%. Tissue-target distance 12.5 cm.)

Dose in r	Time of Irradiation	Av. Latent Period in Days	Takes (per cent)	Initial Tumor Size (cm.)	Av. Growth Period in Days	Max. Tumor Size, Av. Diameter (cm.)	Regressions (per cent)	Remarks
1,100	1′31″	11.0	91.7	0.2 × 0.2	22.0	1.4 × 0.7	25.0	First measurable tumors appeared 9 days, others 15 days after implantation
1,300	1′48″	13.7	86.6	0.4 × 0.3	30.0	1.9 × 1.4	0	First measurable tumors appeared 9 days, others 18 days after implantation
1,500	1′54″	12.6	85.0	0.3 × 0.3	23.0	1.5 × 1.3	20.0	First measurable tumors appeared 12 days, others 14 days after implantation
1,500	2′24″	14.0	78.0	0.4 × 0.3	15.0	0.8 × 0.6	32.5	First measurable tumors appeared 7 days, others 12 days after implantation
1,600	2′27″	14.0	62.5	0.4 × 0.3	13.0	1.0 × 0.9	33.3	First measurable tumors appeared 14 days after implantation
1,800	2′34″	16.5	44.2	0.3 × 0.2	14.7	1.3 × 0.8	48.8	First measurable tumors appeared 9 days, others 14 days after implantation
1,800	2′45″	15.0	48.9	0.4 × 0.4	18.0	0.8 × 0.6	54.5	First measurable tumors appeared 15 days after implantation
1,900	2′43″	17.5	29.1	0.6 × 0.3	16.0	1.1 × 1.0	50.0	First measurable tumors appeared 11 days, others 18 days after implantation
2,000	3′ 4″	18.0	5.5	0.2 × 0.2	18.0	0.5 × 0.3	73.8	First measurable tumors appeared 18 days after implantation
2,200	3′36″	19.0	4.1	0.3 × 0.2	11.0	0.8 × 0.4	100	Only 1 tumor appeared 19 days after implantation. This disappeared eventually

The growth period—*i.e.*, the time elapsing from the first measurement of the tumor following the latent period to the beginning of ulceration or regression—showed no clear-cut relation to the dose of radiation. For example, in the experiment with 1,100 r applied in a period of 23 minutes 5 seconds the average growth period was 29 days, while in the experiments with 1,800 r applied during 40 minutes 32 seconds in one instance and 41 minutes in another the average growth periods were nineteen days and twenty-five days despite the fact that the dose was the same and the period of exposure approximately the same. Hence, it can be said that this growth factor is reproducible only to a certain extent under the same experimental conditions. The same is true of other growth characteristics. For example, with 1,800 r in one instance 75 per cent and in another instance 83 per cent of tumors underwent regression. Further, on analysis of the average tumor sizes, particularly the maximum, it is noted that with a dose of 1,600 r the maximum size is 0.9 × 0.6 cm., while with 1,800 r

TABLE III: CONTROL MICE WITH SARCOMA 180
(No regressions)

Av. Latent Period in Days	Takes (per cent)	Initial Tumor Size (cm.)	Av. Growth Period in Days	Max. Tumor Size, Av. Diameters (cm.)
8	100	0.9 × 0.8	9	2.1 × 1.5
7	98	1.2 × 0.9	12	2.4 × 1.8
7	100	1.1 × 1.0	10	2.6 × 1.6
7	100	0.8 × 0.5	14	2.8 × 1.3
7	100	0.6 × 0.6	14	2.2 × 1.1
7	100	0.6 × 0.4	15	2.3 × 1.3
7	100	1.0 × 0.7	10	2.8 × 1.7
7	100	1.3 × 0.9	12	3.5 × 2.5
8	100	0.7 × 0.6	14	2.6 × 1.9
7	100	0.9 × 0.6	13	2.7 × 1.9

TABLE IV: DIFFERENCE IN EFFECTS PRODUCED BY HIGH AND LOW DOSAGE RATES OF FILTERED 200 KV. X-RAYS

	High Dosage Rate Tissue-target distance 12.5 cm.			Low Dosage Rate Tissue-target distance 50.0 cm.			Difference with Low Dosage Rate		
Dose in r	Average Latent Period in Days	Takes (per cent)	Regressions (per cent)	Average Latent Period in Days	Takes (per cent)	Regressions (per cent)	Latent Period in Days	Takes (per cent)	Regressions (per cent)
1,100	11.0	91.7	25.0	9.0	85.0	25.0	−2.0	− 6.7	0
1,300	13.7	86.6	..*	10.8	84.5	32.5	−2.9	− 2.1	+32.5
1,500†	13.3	81.0	26.3	11.5	76.4	47.2	−1.8	− 4.6	+20.9
1,600	14.0	62.5	33.3	12.8	50.0	50.0	−1.2	−12.5	+16.7
1,800†	16.5	46.5	48.8	14.9	41.2	75.0	−1.6	− 5.3	+26.2
1,900	17.5	29.1	50.0	16.0	14.2	83.0	−1.5	−14.9	+33.0
2,000	18.0	5.5	73.8	17.0	5.5	100	−1.0	0	0
2,200	19.0	4.1	100.‡	0	0	0	.....	......	......

* Percentage of regression not certain, due to early death.
† Average of two experiments.
‡ Only one tumor occurred, which eventually regressed.

the maximum in one instance is 1.1 × 0.8 cm. and in another 0.7 × 0.6 cm. It should be emphasized, however, that the average tumor sizes were derived from unequal numbers of tumors, despite the fact that an equal number of animals was used for each experiment. This was due to variations in percentages of takes and regressions following a given dose of radiation. It is difficult to offer an explanation for this phenomenon unless we assume that the tumor originated from cells of uneven vitality. This assumption can be supported by the fact that the growth period varied markedly among individual tumors; on the other hand, some of the tumors started to regress or ulcerate while others continued to proliferate.

The average tumor growth period for the control mice, as recorded in Table III, varied over a small range, mostly between twelve and fourteen days following the first measurements after the latent period, which was about seven days. This fact indicates that the control tumor fragments were of a more even viability than the irradiated fragments. The narrow range of variation in the maximum tumor size in the control mice supports this fact. Consequently, a given dose of x-rays does not exert a uniform effect on all the cells. The constant latent period of seven days among the control mice, following which tumors of a measurable size occurred, is another evidence of the more even viability of the implanted tumor fragments. This is contrary to the observations on the irradiated tumor fragments, which produced tumors during various intervals of time following implantation.

Table II records the results obtained from experiments which were set up on the same days as those recorded in Table I, using the same experimental procedure, the only difference being that the tumor fragments were exposed for a shorter time to a given total dose of radiation by using a shorter tissue-target distance to obtain a higher dosage rate. The growth factors, as represented by the latent period, percentage of takes, regression of tumors, etc., were affected by given doses of radiation in a similar range as when the same total doses were administered over a longer time, *i.e.*, with the increase of the x-ray dose, there were a decrease in percentage of takes, an increase in the latent period, and an increase in the percentage of regressions.

Similar variations in tumor sizes (initial and maximum) as well as in the prolonged latent periods, etc., which have no relation to the total dose of radiation, can be noted here, as in Table I. An inter-

TABLE V: DIFFERENCE IN PERCENTAGE OF INITIAL MEASURABLE TUMORS PRODUCED BY HIGH AND LOW DOSAGE RATES OF FILTERED 200 KV. X-RAYS

	High Dosage Rate Tissue-target dist. 12.5 cm.		Low Dosage Rate Tissue-target dist. 50.0 cm.		Difference with Low Dosage Rate	
Dose in r	Minimum Latent Period in Days	Initial Measurable Tumors (per cent)	Minimum Latent Period in Days	Initial Measurable Tumors (per cent)	Initial Takes (per cent)	First Latent Period in Days
1,100	7	55.0	7	41.7	−13.3	0
1,300	7	33.3	7	28.0	− 5.3	0
1,500	9	25.0	11.0	19.5	− 5.5	+2
1,600	9	18.5	11.0	14.8	− 3.7	+2
1,800	12	17.0	12.0	11.5	− 5.5	0
2,000	16	3.0	16.0	2.0	+ 1.0	0

pretation of these phenomena has been offered in the discussion of that table. An analytical comparison, however, of the corresponding figures in the two tables, particularly as to the latent period, percentages of takes, and regressions, reveals small but rather constant differences.

These differences are set forth in Table IV. A slightly shorter latent period, a lower percentage of takes, and a greater percentage of regressions occurred, in most instances, with the low dosage rate. Although these figures do not correspond directly to the dose administered, they are, however, always less than with the higher dosage rate. For example, on comparing percentages of regression it can be seen that, with a dose of 1,300 r given at a low rate, 32.5 per cent more tumors regressed than with the high dosage rate, while with 1,800 r the difference was 26.2 per cent. It should be emphasized that these figures represent average results obtained from numerous individual cases within the range of effective dosage. The greater effect of the low dosage rate on the number of takes and the latent period was particularly noticeable in a study of the initial measurements of the tumors, *i.e.*, following the first latent period. These data are included in Table V and illustrated in the accompanying graph (Fig. 1) Although no clear-cut relation between the percentage of takes and the dose of radiation can be noted, the differences are nevertheless constant. For example, with a dose of 1,100 r 13.3 per cent less takes occurred with the low dosage rate, while with 1,600 r 3.7 per cent and with 1,800 r 5.5 per cent less takes occurred as compared with those obtained with the high dosage rate.

More complicated are the observations made in regard to the latent period. As was pointed out in the discussion of the foregoing tables, an initial and delayed latent period occurred which varied markedly in each experiment. This phenomenon makes it difficult to draw definite conclusions. The averages of both latent periods (initial and prolonged), as shown in Table IV, are slightly shorter with the low dosage rate, contrary to the average initial latent period recorded in Table V, which in some instances is slightly longer.

The more marked effects of irradiation with a low dosage rate seemed to appear with the more effective doses; no marked differences can be noticed with the less effective doses or the lethal doses, as compared with results obtained with a high dosage rate. Within the sublethal or critical dosage levels a sudden drop in takes occurs with the low as well as with the high dosage rate. The critical dosage levels in these experiments were found to be between 2,000 and 2,200 r with both dosage rates. Starting with doses of about 1,000 r up to 2,200 r the growth characteristics could be followed comparatively, to a certain extent, for the two dosage rates, high and low. With doses above 2,200 r, with both high and low dosage rates, one or two tumors developed after a long latent period of about eighteen to twenty days, which in some instances eventually regressed. Since the main interest of these experiments was not to determine the absolute lethal dose of x-rays for this type of tumor, which has been done by other investigators (2, 3, 4), but rather to determine the effects upon the growth characteristics produced by two different dosage rates, the results

recorded here are limited to these observations.

EXPERIMENTS WITH UNFILTERED 45 KV. X-RAYS

For these experiments the Philips-Metalix[2] contact therapy machine was used, the physical factors being 45 kv., 2 ma., with an inherent filtration of 0.2 mm. Al, and a half-value layer of 0.28 mm. Al, no external filter. By using a tissue-target distance of 1.82 cm. and 7.22 cm., corresponding dosage rates of 5,750 r/min. ±10 per cent and of 365 r/min. ±10 per cent were obtained as measured in air. (The ±10% was the difference of rate for various experiments.) The ratio of the time factor in each experiment was 1:16. The type of tumor tissue and the experimental procedure were as described in the foregoing experiments with filtered 200 kv. x-rays. Some of these experiments were carried out simultaneously with those with filtered x-rays, tissue from the same tumors being used.

For clarity it may be repeated that for each experiment 8 to 12 mice were injected in both axillae with approximately the same amount of irradiated sarcoma fragments, suspended in saline solution. An equal number of mice were used as controls. The main observations made from these experiments are recorded in Tables VI and VII. It should again be emphasized that the data recorded represent averages of repeated experiments carried out with the same total doses. Besides those recorded, numerous experiments were carried out with lower and higher doses. Since the results obtained with lower and intermediate doses did not reveal any marked differences in the effects, it was not deemed necessary to include them here.

Analysis of the data recorded in Tables VI and VII reveals observations similar to those in the experiments with filtered x-rays, *i.e.*, a decrease in percentage of takes and an increase in the latent period as well as in the percentage of regressions, corresponding roughly to the dose of radiation administered to the tumor fragments. The effectiveness of radiation upon these growth factors seemed to begin

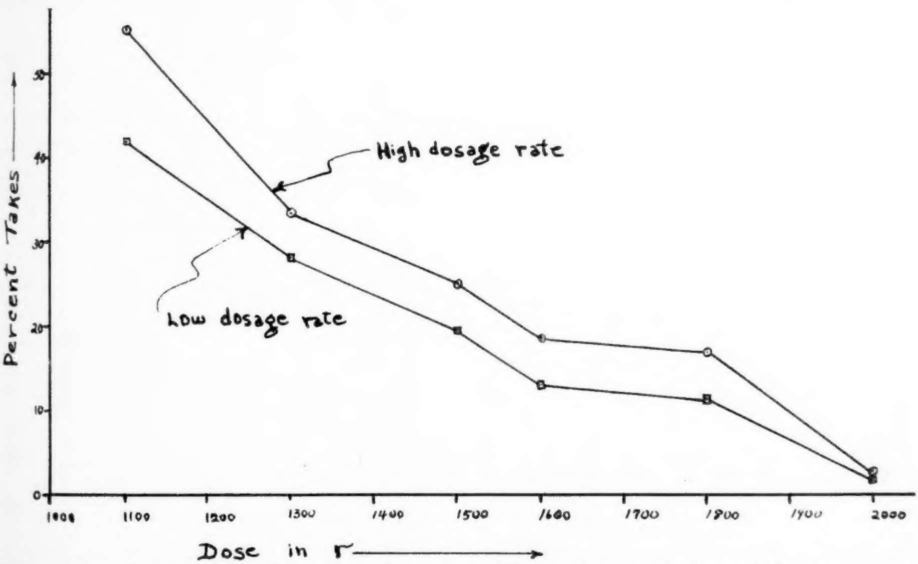

Fig. 1. Curves derived from Table V, showing a constant difference between the low and high dosage rates in variation of initial percentages of takes, with the dose in r.

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[2] I wish to express my sincere gratitude to the Philips-Metalix Company for the loan of this x-ray generator for these experiments.

TABLE VI: EFFECTS OF UNFILTERED 45 KV. X-RAYS UPON GROWTH FACTORS IN VIVO OF MOUSE SARCOMA 180
(Dosage rate 5,750 r/min. ±10%. Tissue-target distance 1.82 cm.)

Dose in r	Time of Irradiation	Av. Latent Period in Days	Takes (per cent)	Initial Tumor Size (cm.)	Av. Growth Period	Maximum Tumor Size: Av. Diameter (cm.)	Regressions (per cent)	Remarks
800	8.6″	7.4	78.6	0.6 × 0.3	14.4	1.5 × 0.8	5.0	Some measurable tumors appeared 7 days, others 9 days after implantation
1,000	10.4″	9.5	68.9	0.5 × 0.5	18.0	1.0 × 0.6	14.8	Some measurable tumors appeared 7 days, others 12 days after implantation
1,200	12.6″	11.5	57.5	0.4 × 0.2	13.3	1.2 × 0.8	28.0	First measurable tumors appeared 9 days, last one 17 days after implantation
1,400	14.7″	9.0	43.7	0.3 × 0.3	20.0	1.0 × 0.6	42.8	First measurable tumors appeared 10 days, others 15 days after implantation
1,600	17.0″	12.5	42.8	0.5 × 0.4	13.5	0.9 × 0.7	48.5	First measurable tumors appeared 10 days, others 15 days after implantation
1,800	18.9″	14.0	28.6	0.4 × 0.3	14.5	1.5 × 1.2	15.0	All measurable tumors appeared 14 days after implantation
2,000	20.8″	15.0	14.3	0.3 × 0.2	16.0	1.0 × 0.9	100	First measurable tumor appeared 13 days, other 17 days after implantation

TABLE VII: EFFECTS OF UNFILTERED 45 KV. X-RAYS UPON GROWTH FACTORS IN VIVO OF MOUSE SARCOMA 180
(Dosage rate 360 r/min. ±10%. Tissue-target distance 7.22 cm.)

Dose in r	Time of Irradiation	Av. Latent Period in Days	Takes (per cent)	Initial Tumor Size (cm.)	Av. Growth Period in Days	Max. Tumor Size, Av. Diameter (cm.)	Regressions (per cent)	Remarks
800	2′14″	8.0	70.0	0.5 × 0.4	16.0	1.2 × 0.6	11.0	Some measurable tumors appeared 7 days, others 9 days after implantation
1,000	2′48″	9.5	50.0	0.4 × 0.3	14.4	1.1 × 0.8	12.0	Some measurable tumors appeared 7 days, others 12 days after implantation
1,200	3′22″	8.0	68.7	0.5 × 0.3	21.0	1.2 × 0.7	27.5	First measurable tumors appeared 7 days, others 12 days after implantation
1,400	4′29″	8.5	45.0	0.4 × 0.3	15.3	0.8 × 0.6	50.0	Some measurable tumors appeared 7 days, others 9 days after implantation
1,600	4′38″	13.0	25.0	0.3 × 0.3	13.0	1.1 × 1.0	69.8	First measurable tumors appeared 13 days after implantation
1,800	4′58″	17.5	14.2	0.4 × 0.4	14.0	0.9 × 0.9	85.0	First measurable tumors appeared 15 days, others 20 days after implantation
2,000	5′28″	19.0	7.1	0.4 × 0.3	17.0	1.0 × 0.8	100.0	Only 1 of 14 implants developed a tumor, which eventually regressed

with lower doses in these experiments than in those with 200 kv. filtered x-rays. For example, with a dose of 800 r (with both high and low dosage rates) a decrease of about 30 per cent in takes occurred. Also, 8 per cent of regressions were observed as compared with the control mice. Similar effects upon these growth factors first appeared with doses of about 1,000 to 1,200 r of filtered x-rays. Within

TABLE VIII: DIFFERENCE IN EFFECTS PRODUCED BY HIGH AND LOW DOSAGE RATES OF UNFILTERED 45 KV. X-RAYS

	High Dosage Rate Tissue-target dist. 1.82 cm.			Low Dosage Rate Tissue-target dist. 7.22 cm.			Difference with Low Dosage Rate		
Dose in r	Average Latent Period in Days	Takes (per cent)	Regressions (per cent)	Average Latent Period in Days	Takes (per cent)	Regressions (per cent)	Latent Period in Days	Takes (per cent)	Regressions (per cent)
800	7.4	78.6	5.0	8.0	70.0	11.0	+0.6	− 8.6	+ 6.0
1,000	9.5	68.9	14.8	9.5	50.0	12.0	0	−18.9	− 2.8
1,200	11.5	57.5	28.0	8.0	68.7	27.5	−3.5	+11.2	+ 0.5
1,400	9.0	43.7	42.8	8.5	45.0	50.0	−0.5	+ 1.3	+ 7.2
1,600	12.5	42.8	48.5	13.0	25.0	69.8	+0.5	−17.8	+21.3
1,800	14.0	28.6	50.0	17.5	14.2	85.0	+3.5	−14.4	+35.0
2,000	15.0	14.3	100	19.0	7.1	100	+4.0	− 7.2	0

the critical doses, however, no marked differences in the effectiveness could be observed between filtered and unfiltered x-rays. On analyzing further the data included in Tables VI and VII there can also be noted two different latent periods occurring in the same experiment, an initial and a prolonged, *i.e.*, some tumors, although small but of a measurable size, appeared seven days and others ten to fifteen days after implantation. Similar variations in the initial as well as in the maximum tumor sizes, not related directly to the dose of radiation applied or to the dosage rate, can be noted here as in the foregoing experiments. A tentative explanation of these phenomena has already been offered.

The data obtained with the low and high dosage rates of the 45 kv. unfiltered x-rays are similar to the results with the two different dosage rates of 200 kv. x-rays where the time ratio was the same, *i.e.*, 1:16. With only one or two exceptions, a smaller percentage of takes and a larger percentage of regressions occurred with the lower dosage rate as compared with the higher dosage rate, when the total dose of x-rays was the same. The decrease in percentages of takes and the increase in percentages of regressed tumors do not correspond directly to the dose applied but, as stated above, this phenomenon appeared in most instances.

TABLE IX: DIFFERENCE IN PERCENTAGE OF INITIAL MEASURABLE TUMORS PRODUCED BY HIGH AND LOW DOSAGE RATES WITH UNFILTERED 45 KV. X-RAYS

	High Dosage Rate Tissue-target dist. 1.82 cm.		Low Dosage Rate Tissue-target dist. 7.22 cm.		Difference with Low Dosage Rate	
Dose in r	Minimum Latent Period in Days	Initial Measurable Tumor (per cent)	Minimum Latent Period in Days	Initial Measurable Tumor (per cent)	Initial Takes (per cent)	First Latent Period in Days
800	7.0	44.0	7.0	25.0	−19.0	0
1,000	8.0	25.0	8.0	15.3	− 9.7	0
1,200	8.0	18.7	8.0	15.0	− 3.7	0
1,400	8.0	25.0	10.0	12.5	−12.5	+2
1,600	10.0	15.9	12.0	9.8	− 6.1	+2
1,800	12.0	13.5	12.0	12.8	− 0.7	0
2,000	12.0	8.8	16.0	5.0	− 3.8	+4

On comparing the average latent periods with the two dosage rates, no clear-cut results can be seen. In the majority of cases, however, a slight increase in the average latent period occurred with the low dosage rate. The differences in the effects produced by the high and low dosage rates upon the average latent period, percentage of takes, and percentage of regressions are illustrated in Table VIII. In the majority of instances a longer latent period, a smaller percentage of takes, and a greater percentage of regressions occurred with the low dosage rate. More constant results, although not clear-cut, are seen

in Table IX, which contains the initial latent periods and the initial measurements of the tumors which occurred with both high and low dosage rates. The initial percentage of takes was smaller with the low dosage rate in all instances. The initial latent periods vary: in some instances no difference occurred, while in others there was a slightly longer latent period with the low dosage rate. These results substantiate to a certain extent those included in Table V, which were obtained with filtered 200 kv. x-rays, using

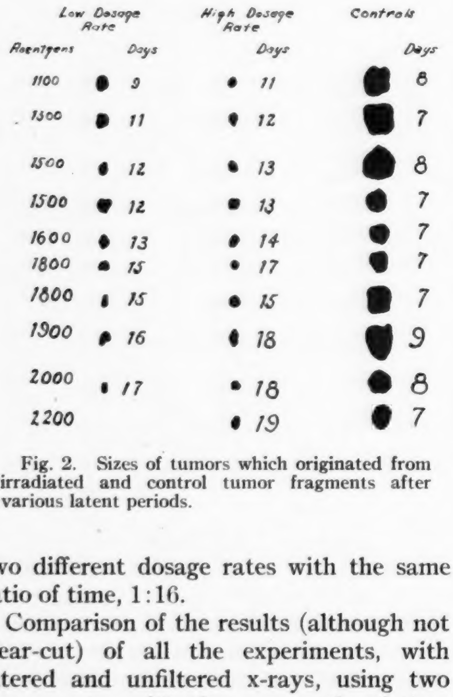

Fig. 2. Sizes of tumors which originated from irradiated and control tumor fragments after various latent periods.

two different dosage rates with the same ratio of time, 1:16.

Comparison of the results (although not clear-cut) of all the experiments, with filtered and unfiltered x-rays, using two dosage rates with the same ratio of time (1:16), shows that greater effects upon the growth characteristics mentioned above were exerted by a given total dose of radiation administered at a low rate than at a high rate. These observations were made within the range of effective doses—1,000 to 2,200 r of filtered and 800 to 2,000 r of unfiltered x-rays. With higher doses at both rates, one or two small tumors developed following a latent period of eighteen to twenty days. In such cases, no comparative results on the growth characteristics could be followed.

SUMMARY AND DISCUSSION OF RESULTS

These experiments were undertaken in an attempt to evaluate the relation of the time factor to the effectiveness of irradiation produced by a given dose of x-radiation.

An increase in the latent period, a decrease in percentage of takes, and an increase in percentages of regressed tumors occurred, corresponding roughly to the increase of the effective dose of radiation administered. These phenomena were observed with both types of irradiation, filtered and unfiltered, using both high and low dosage rates. A comparison of the effects upon the growth characteristics produced by the same total dose of x-rays (both filtered and unfiltered) with different dosage rates reveals the following: A lower percentage of takes occurred and a greater percentage of tumors underwent regression after a given total dose of x-rays with the low dosage rate than with the high dosage rate. Although the differences were small in some instances and not proportional, they were, however, constant. The difference in effects produced by the two dosage rates was more apparent within the range of 1,000 to 2,200 r. No marked difference in the effects produced by the high and low dosage rates could be observed with less effective dosages, below 1,000 r and above 2,200 r. A sudden drop in takes was manifested within the critical dosage levels with both types of irradiation and with both dosage rates, high and low. A tentative explanation of these phenomena is offered. With less effective doses a recovery or restitution of the disorganized cells may take place, regardless of the dosage rate; with critical doses, however, recovery processes are very limited. The time factor has no significance in these cases. Within the effective dose range, on the other hand, the influence of the time factor is exerted over a longer period, during which a larger number of cells may pass into a phase of

mitosis when they are more radiosensitive. Thus a larger total number of cells may be destroyed for a given amount of radiation when the period of exposure is longer.

No clear-cut observations as to the latent period were made. In some instances a longer latent period was observed with the high dosage rate, in others a slightly shorter; particularly was this so of the average figures for the initial and prolonged latent periods, which are discussed in the text. A comparison of the initial latent periods for the two rates (high and low) shows, however, a slightly longer latent period with the low rate. On the other hand, it was shown that the latent period is quite dependent upon the total dose of radiation administered to the tumor fragments. With the increase of the effective dose, an increase particularly in the initial latent period occurred.

Variable observations were made in regard to maximum tumor sizes. Some tumors attained larger and some smaller dimensions, regardless of either the total dose of radiation or the dosage rate. The rate of growth, however, was retarded in all cases when an effective dose of x-ray was applied, as compared to the control tumors. In some instances, though the rate of growth was slower, the tumor eventually reached a size corresponding to that of a control tumor.

When between 2,000 and 2,200 r of filtered and unfiltered x-rays were given with either dosage rate, small tumors developed after a long latent period, as for example eighteen to twenty days. These tumors in most instances eventually regressed. These doses—2,000 to 2,200 r—should, in our opinion, be regarded as critical doses, particularly when the size of tissue fragments is very small.

Sugiura (2) did not observe any apparent difference in the percentage of takes of sarcoma 180 after using dosage rates of filtered x-rays with a time ratio of 1:5. This discrepancy may be explained by the fact that the experiments discussed in this paper were carried out with a time ratio of 1:16. Another thing which may have influenced this difference in results is the fact that Sugiura used tumor fragments for irradiation about three times as thick as those used in the experiments here described. With very thin tissue fragments the attenuation of the primary beam of x-rays is less than with thicker fragments, resulting in a more uniform distribution of the absorbed radiation within the tissue. A greater effect, therefore, may be expected from the same total dose.

A slight deviation from the Bunsen-Roscoe law in the effects of x-rays on living cells is observable within certain limits, *i.e.*, within the range of critical doses, where a recovery of cells or a reversibility of the effects is still possible.

From a comparison of the periods of exposure for a given dose of x-radiation, particularly within the critical dosage levels (2,000 to 2,200 r), the following statement may be made. Similar effects upon growth characteristics were produced by total doses applied during 3 minutes 36 seconds at a dosage rate of 650 r/min., during 51 minutes 12 seconds at a dosage rate of 40 r/min. (filtered x-rays), during 20.8 seconds at a dosage rate of 5,750 r/min., and during 5 minutes 28 seconds at a dosage rate of 360 r/min. (unfiltered x-rays). These figures indicate that the biological effects of irradiation depend upon the dosage rate and time of exposure. It seems that a combination of the proper dose with a proper rate of administration, providing a sufficient quantity of radiant energy to destroy all vital processes within the cells, regardless of their stage of mitosis, is necessary to obtain the desired results.

The observations made in these experiments substantiate to a certain extent those from previous *in vitro* experiments (1). In the present experiments an attempt was made to combine *in vitro* and *in vivo* experiments, using the same type of tumor. Irradiation of the freshly excised tumor fragments took place *in vitro* in both sets of experiments, but in the present series the irradiated tumor fragments were implanted into the axillae of mice instead of into a

culture medium. The critical doses for the proliferation of sarcoma 180 grown *in vitro* were found to be between 50,000 and 60,000 r of filtered 200 kv. x-rays, at a dosage rate of 936 r/min. with exposure times of 53 to 64 minutes, respectively. Similar effects were obtained with the Philips-Metalix contact therapy machine, with exposure times of $8^1/_2$ to 9 minutes, and a dosage rate of 5,750 r/min., resulting in doses of 48,000 to 52,000 r. It should be recorded here that in reviewing our previous work (1) it was found that the actual dosage rate in those experiments was about 5,750 r/min. and not 10,000 r/-min. as was stated.

The critical doses for proliferation *in vivo* following irradiation *in vitro* of the same type of tumor were found to be between 2,000 and 2,200 r with both filtered and unfiltered irradiation, using two dosage rates with a time ratio 1:16. The question why a much higher dose of radiation is necessary to effect proliferation *in vitro* than proliferation *in vivo* is being repeatedly raised. Just as the biological effects of irradiation are complex, so is the culture medium *in vivo* in which proliferation takes place. Proliferation *in vitro* takes place in a medium free from lymph, blood, hormones, and other factors regulating living processes, and it is also limited to a small area, containing a small number of cells as compared to a whole tumor, which is a living system in itself. Further, observations on growth *in vitro* can be made one or two days following transplantation, while at least a week must elapse before a palpable tumor can be observed *in vivo*. During this time various mutation processes may have occurred among the irradiated cells, and the tumor produced may consist of cells of different biological characteristics than the original cells before or shortly after irradiation. The regression of tumors originating from irradiated cells can be explained by this process.

Whether the results obtained in these experiments are applicable to spontaneous tumors remains to be proved. It should be remembered that the dose of radiation to the transplantable tumor tissue used in these experiments was applied *in vitro* before implantation into the animal. Further experiments to throw some light on this question are in progress.

My sincere thanks are herewith expressed to Carl B. Braestrup, senior physicist, and to Gordon H. Cameron, assistant physicist, Department of Hospitals, New York City, for their helpful co-operation. I also wish to thank the W. P. A. for assigning a technical assistant for these experiments.

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Depth Dosage Measurements by Means of Goldfish[1]

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NUMEROUS methods have been employed in approaching a clinical evaluation of the action of roentgen rays. Biological methods permit qualitative as well as quantitative determinations of the effects of radiation. Physical methods enable us to calculate the r units delivered to a certain volume of tissue.

One of the outstanding tasks of experimental radiation therapy is the correlation of physical doses with biological effects. In so far as the effects of roentgen and gamma rays on the surface are concerned, this correlation has been achieved fairly satisfactorily. Various reactions with various test objects, such as the skin erythema, the lethal effects on seedlings, ova, tissue cultures, etc., are at our disposal for the study of these surface effetcs. The biological evaluation of the effects of roentgen rays in the depths has, however, encountered certain difficulties.

Because of the large percentage of water in the make-up of the human body, the water phantom is commonly used by the physicist for depth dose measurements (3, 13). Two principal obstacles have had to be dealt with in the performance of biological experiments in the depths of this phantom: (1) the difficulty of providing an adequate oxygen supply to the test object; (2) the necessity of wrapping the test object for its protection against water. The deficiency of oxygen affects the vitality of the test object and the wrapping material may change the radiation by absorption.

Due to the progressive technical improvements in equipment, with the production of more and more penetrating radiation, interest has been focused on the problem of its biological action in the depths (1–15). Because of the lack of uniformity in existing data (16–25), it appeared worth while to try a biological test object not hitherto used for this purpose, which could be of value in the investigation of the effects of different qualities of radiation both on the surface and in the depths of a water phantom. With the disturbing factors in depth dose measurements mentioned above in mind, the common goldfish (*Carassius auratus*) was chosen, since water is its natural habitat.

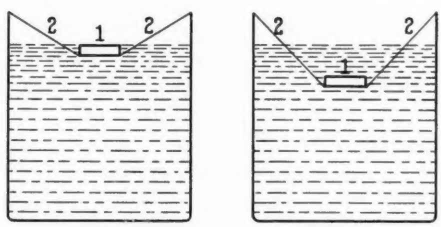

Fig. 1. Method of irradiation. The drawing on the left shows the surface, or zero, position. The Petri dish (1) rests on a layer of gauze (2) suspended flush with the surface of the water in the phantom. The right-hand drawing shows the Petri dish submerged for depth irradiation. The depth is measured from the surface of the water in the phantom to the upper margin of the dish.

In previous investigations we have demonstrated the suitability of the goldfish for the biological evaluation of roentgen radiation on the surface of the water phantom (26). Goldfish are equally suitable for the biological evaluation of the action of different qualities of roentgen rays in the depths of the water phantom, as will be shown.

TECHNIC OF IRRADIATION

The technic of irradiation in the present experiments was the same as in our previous investigations and may be illustrated by Figure 1. For each exposure 12 fish were placed in an open Petri dish, 15 cm. in

[1] From the Radiotherapy Department, Montefiore Hospital for Chronic Diseases, New York. Presented before the Radiological Society of North America at the Twenty-sixth Annual Meeting, Cleveland, Ohio, Dec. 2-6, 1940.

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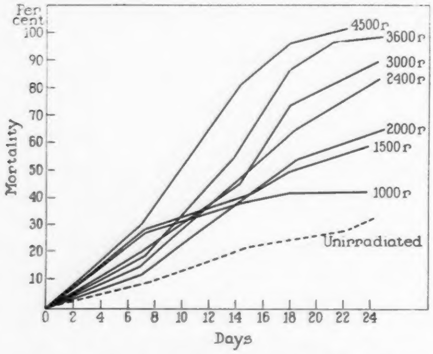
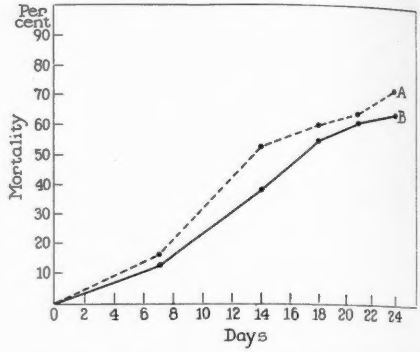


Graph 1. Mortality curves for 534 fish irradiated at 10 cm. depth with doses of 1,000 to 4,500 r/air (H.V.L. 0.9 mm. Cu), showing increased mortality with increased radiation dosage.



Graph 2. Comparison of two ionometrically equal doses. (A) H.V.L. 0.233 mm. Cu, depth dose 22 per cent, 3,000 r/air = 600 r at 10 cm. (B) H.V.L. 0.9 mm. Cu, depth dose 34 per cent, 2,000 r/air = 680 r at 10 cm.

diameter, covered with a single layer of gauze fixed by an elastic band. In the surface position the dish rested on a layer of gauze suspended flush with the surface of the water in the phantom. For the study of the action in the depths the dish was submerged to the desired depth measured from the surface of the water in the phantom to the upper margin of the Petri dish.

The phantom, measuring 32 × 32 × 32 cm., permitted the maximum backscatter according to determinations of Quimby and co-workers (27).

The radiation factors were as follows. (A) 200 kv., 30 ma. (mechanical rectification), no filtration, H.V.L. 6.0 mm. Al, corresponding to 0.233 mm. Cu, intensity 230–172 r/min.; (B) 200 kv., 25 ma., 0.5 mm. Cu and 3.0 mm. Al filtration, H.V.L. 0.9 mm. Cu, intensity 58 r/min. The target distance was 50 cm.; the field 15 × 15 cm. Doses of 500–10,000 r (measured in air) were given in one session.

The ionization measurements were made with a Victoreen condenser r-meter, in co-operation with Miss L. Jacobson, our physicist.

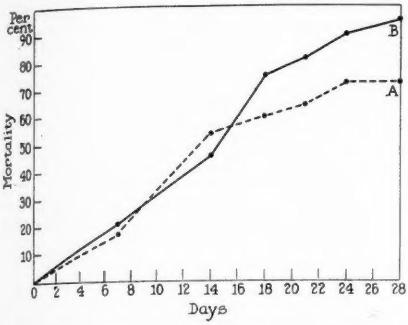
The depth dose at 10 cm. was related to the zero position of our experiments. The chamber rested on the bottom of the Petri dish, which was suspended flush with the surface of the water in the phantom. The dish and chamber were then submerged to 10 cm. depth.

The data obtained from observation of 2,456 fish, of which 587 served as unirradiated controls, are presented graphically.

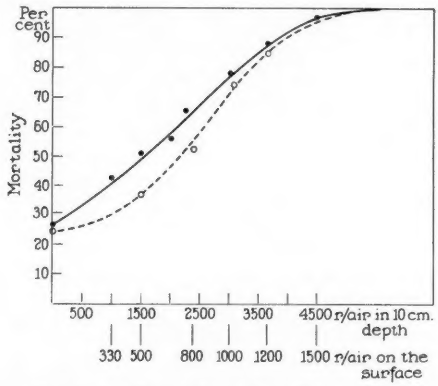
Graph 1 shows that at 10 cm. depth, just as on the surface, the mortality increased with increased doses of roentgen radiation.

Graph 2 shows the effect of two ionometrically equal doses at 10 cm. depth. Curve A represents the effect of radiation of H.V.L. 0.233 mm. Cu. The depth dose is 22 per cent so that when 3,000 r/air were given, fish suspended at 10 cm. depth received an effective depth dose of 660 r (calculated). Curve B represents the effect of radiation of H.V.L. 0.9 mm. Cu, depth dose 34 per cent. When 2,000 r/air were given to the fish in 10 cm. depth, they received an effective depth dose of 680 r (calculated). As can be seen, the curves show the equal effect of ionometrically equal doses.

Graph 3 illustrates the effects of two ionometrically unequal doses. Curve A shows the effect of 3,000 r/air, H.V.L. 0.233 mm. Cu, depth dose 22 per cent, which is equal to 660 r at 10 cm. depth, while Curve B represents the effect of 3,000 r/air, H.V.L. 0.9 mm. Cu, depth dose 34 per cent, which is equal to 1,020 r at



Graph 3. Comparison of two ionometrically unequal doses, showing greater lethal effect of the greater depth dose. 3,000 r/ in air, 10 cm. depth. (A) H.V.L. 0.233 mm. Cu, depth dose 22 per cent. (B) H.V.L. 0.9 mm. Cu, depth dose 34 per cent.



Graph 4. Comparison of surface and depth effects (mortality curves for 18th day) of ionometrically equal doses. The broken line represents the effects of radiation (H.V.L. 0.233 to 0.9 mm. Cu) on the surface (1,920 fish). The solid line represents the effects of radiation (H.V.L. 0.9 mm. Cu) at a depth of 10 cm. (534 fish).

10 cm. depth. As can be seen, radiation B, with the higher depth dose, also shows the greater lethal effect.

These three demonstrations seem to prove the suitability of goldfish for the biologic evaluation of roentgen rays in the depths, at least so far as the problem of greater or less effectiveness is concerned.

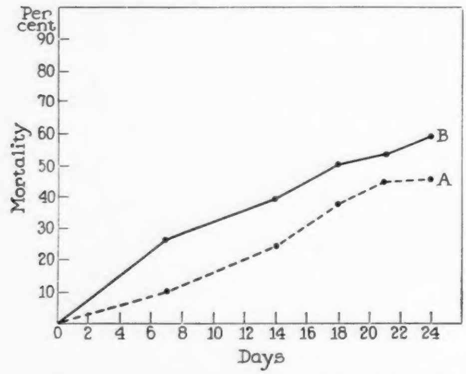
The quantitative aspect of this problem will now be considered. Study along this line is facilitated considerably by using mortality curves. Previous investigations have revealed an S-shaped mortality curve for the effects on the surface (26). Such curves are well known from studies on smaller objects, such as egg cells. The importance of these curves consists in the fact that a change in their shape indicates a difference in biological action (28).

In Graph 4 the broken line represents the surface effect, as established in previous investigations, based on the observation of 1,920 fish. No change in the shape has been found for different wavelengths. Over this curve the mortality curve for radiation (H.V.L. 0.9 mm. Cu) at 10 cm. depth is superimposed. The abscissa values in this chart are calculated according to the ionometrically measured depth dose of 34 per cent. According to these calculations the effects of 1,500 r/air at 10 cm. depth and that of 500 r/air on the surface should be identical, etc. As can be seen, however, there is a considerable deviation in the shape of the curves. This means that ionometrically equal doses show a different biological effect at 10 cm. depth.

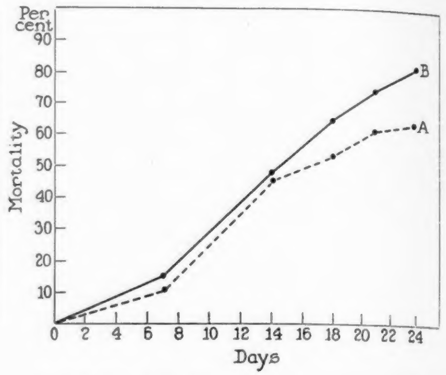
Graphs 5, 6, and 7 may serve for further analysis. In Graph 5 curve A shows the lethal effect of 500 r/air, H.V.L. 0.9 mm. Cu, given to fish at the surface of the water phantom, while curve B shows the lethal effect of 1,500 r/air of the same radiation given to fish at 10 cm. depth. On the basis of an ionometrical depth dose of 34 per cent, the effects should be equal. This, however, is not the case. A greater effect is seen in the depths.

Graph 6 shows conditions for 800 r/air on the surface and 2,400 r/air at 10 cm. depth for the same radiation. This graph, again, exhibits a greater lethal effect in the depths.

From Graph 7, some information may be gathered concerning the amount of increase in the biological activity in the depths. Curve A represents the lethal effect of doses of 670 r effective in 10 cm. depth (without considering the wavelength) while curve B represents the effect of 800 r/air (without considering wavelength) when given to fish on the surface of the water phantom. As can be seen, these curves correspond completely. For this particular case, therefore, we may estimate



Graph 5. A. Effect of 500 r/air at surface. B. Effect of 1,500 r/air at 10 cm. with H.V.L. 0.9 mm. Cu, depth dose 34 per cent, equivalent to 500 r at surface.



Graph 6. A. Effect of 800 r/air at surface. B. Effect of 2,400 r/air at 10 cm. with H.V.L. 0.9 mm. Cu, depth dose 34 per cent, equivalent to 800 r at surface.

the increase in biologic activity in the depth as about 20 per cent. Histologic studies of the brains of irradiated goldfish[2] seem to substantiate the increased biological activity. This, however, will be covered in a later paper.

COMMENTS

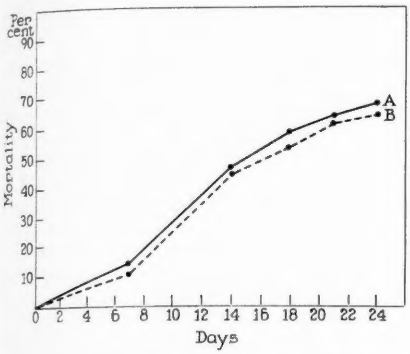
It may be added that the demonstrated change in the shape of the mortality curves for ionometrically equal doses on the surface and at 10 cm. depth in the water phantom is statistically significant. The fact that this phenomenon is more pronounced with smaller doses can easily be understood. No definite explanation, however, can at present be advanced for the greater biological effects in the depths. It is our object merely to draw attention to this phenomenon. The importance of this observation, made on a complex multicellular organism which contains a circulatory system, is emphasized by the fact that it is in agreement with the findings of Packard on the unicellular *Drosophila* eggs (20). Packard has suggested the use of the term "biological roentgen" (29) for the biological evaluation of radiation effects, thus implying that there may not always be complete agreement between ionization and biological effects (10).

[2] In co-operation with Dr. C. Davison of the Neuropathological Laboratory.

Recently, Sievert, physicist to the Radiumhemmet in Stockholm, has reported on the measurement of ionizing radiations. From physical considerations he also came to the conclusion that there is a possibility that ionization and biological effects may not always be in agreement (30). He writes (31):

> "Owing to our lack of knowledge of the mechanism of the biological effects, it is advisable to regard the r-unit as a provisional unit, for as we learn more of the mechanism of the biological effects of radiation, new and quite different demands on radiation units for biological and medical purposes will certainly arise. I believe that in the next few years, research will bring to light so many biological difficulties in estimating the effective dosage that the question of units will become a question of less importance. Obviously there is at present no reasonable proportion between, for instance, the extreme accuracy with which we attempt to determine the dose given and our knowledge of the importance of conditions like, for instance, the time factor and the varying radiosensitivity of tumors. Nor must it be forgotten that we have now, largely by means of the method of protraction and of divided doses (Coutard), reached a new phase in the development of radiotherapy, in which the risk of damage to the skin is no longer of the same importance as formerly."

This quotation from Sievert should not be understood as a proposal on our part to abandon the use of the r unit, which fortunately is now recognized throughout the world and which has contributed to a considerable extent to the advances in



Graph 7. Showing that the lethal effect of a dose ionometrically measured as equal to 670 r at 10 cm. depth corresponds to that of 800 r/air at the surface. A. Effect of 670 r at 10 cm. (154 fish). B. Effect of 800 r at surface (201 fish).

radiology. As shown above, ionization is still a sufficiently reliable indicator for the determination of greater or lesser biologic activity, since in our investigations irradiation with the greater depth dose also showed the greater lethal effect. It may be emphasized, however, that radiations which have different per cent depth doses may exert effects in the depths which are not in direct proportion to the ionometrically measured doses.

It is the intention of this presentation to stress the importance of correlating ionization effects with as many different biologic tests as possible, thus providing a strong and reliable basis for the clinical application of roentgen rays. This is one of the chief tasks of a systematic experimental radiation therapy and paves the way for future clinical developments.

SUMMARY AND CONCLUSIONS

1. The suitability of the goldfish test for the evaluation of different types of radiations in the depths of the water phantom has been demonstrated.

2. While the radiation with the ionometrically measured greater depth dose has also shown a greater biologic depth effect, the proportion of difference between two radiations ionometrically measured and biologically evaluated is not the same, the biologic activity in the depths having been found to be greater than was expected.

3. The data presented emphasize the necessity of corroborating physical data with corresponding changes in as many biologic test objects as possible.

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DISCUSSION

Otto Glasser, Ph.D. (Cleveland): I think this is a very interesting new addition to the study of x-rays by means of biological methods. As I brought out yesterday in my short talk on dosimetry,[1] in the history of the dosimeter, many of the methods have been developed parallel to one another. Biological methods have been used for a number of years. Why do we use biological dosage methods? We have the roentgen unit; we are satisfied that it is as good a physical unit as we can design at the present time, and we feel that it serves all practical purposes. However, we are disappointed that the roentgen unit is based upon the ionization in air. In treatment and in biologic experiments we deal with tissues and we are not yet certain what the correct relationship is between ionization in air and the effects of x-rays upon cells of various types.

Dr. Ellinger brought out the fact that if he measures depth doses with goldfish he obtains apparently a higher percentage depth dosage than by ionization in air. This agrees with other depth dose measurements which have been made in the past upon other biological objects, by Packard and Henshaw.

Furthermore, we experiment with various biological methods because we still feel that there may be some dependence of the biological effects of x-rays upon the radiation quality or wavelength. Although this phase has been worked on for years, we have not arrived at any definite conclusions.

Dr. Ellinger demonstrated that with goldfish there seems to be no noticeable effect of wavelength. That agrees with experiments made by Packard on *Drosophila* eggs.

I am impressed by the various advantages outlined by Dr. Ellinger. A possible disadvantage concerns the accuracy. I noticed that the normal death rate of goldfish is rather high and, perhaps for that reason, Dr. Ellinger has used the total mortality curve in studying the effect instead of the value Packard used, namely, the amount of radiation necessary to kill one-half of *Drosophila* eggs.

In conclusion, it is gratifying to have another biological method to measure x-rays, and one which seems to offer a number of advantages over biological methods used hitherto. I feel that the more methods we have, the better we will be able to study the possible differences between the effects of x-rays upon different biological specimens, and perhaps arrive at some definite conclusion in regard to the correlation between ionization effects in air and the effects produced by x-rays upon various tissues.

Paul S. Henshaw, Ph.D. (National Cancer Institute): Dr. Ellinger is to be congratulated on having the courage to undertake a problem that has been proved before to be difficult. As he has pointed out, the object of his paper was to show that goldfish are equally as suitable as other test objects for the biological evaluation of the action of different qualities of roentgen rays in the depths of the water phantom. This, as far as I am able to judge, he has done in admirable fashion. However, it is my opinion that he has proved equally well that goldfish have limitations as great as the other test objects when it comes to obtaining the information really desired.

Dr. Ellinger has presented his paper under the heading depth dose measurements, which, in last analysis, means wavelength dependence studies of radiobiologic reactions. This is the case, since a correlation was made of the biologic responses with the ionization doses at different depths, and since radiation in passing through a medium such as water undergoes repeated scattering and becomes gradually softer.

The results, as presented, show clearly that the biological responses observed and the ionization measurements as made do not go hand in hand as the phantom depth is varied—that is, as the wavelength or quality of radiation is varied. But we ask, which was it that varied? In going from the lesser to the greater depth, did the biological material show a greater sensitivity, as Dr. Ellinger suggests, or did the ionization chamber fail to detect some ionization that was biologically effective?

It seems to me that the most significant information available which bears on these questions is that recently obtained by the Memorial Hospital group (Drs. Failla, Quimby, Marinelli, etc.). These investigators have determined the threshold erythema dose for human skin for the whole range of radiations varying from 100 kv. to 1,000 kv. x-rays and

[1] See Radiology **37:** 221–227, August 1941.

found it to vary from 250 r to 1,000 r, the higher dosages being associated with the higher voltage radiations. Moreover, these investigators varied the gaseous mixtures in the ionization chambers used to measure the doses in roentgens and found that the nearer the mixtures approximated the ratios of the elements in the skin, the less the differences became. This furnishes ample justification for the suspicion, expressed by Dr. Ellinger toward the end of his paper, that the ionization measurements made in air to be in accord with the roentgen may not have represented the ionization produced in the tissues.

In dealing with the problem of wavelength dependence, a couple of years ago, I pointed out that, in my opinion, two factors must be known before we can expect to obtain a satisfactory solution for any tissue or organism. The first is the size of the sensitive region, and the second is the amount of ionization produced in that region. When we can say precisely what the amount of ionization is at the spot where the changes are produced that lead to the lethal action, then—and I believe only then—shall we be able to say anything about the wavelength dependence of radiobiologic reactions.

From all appearances, it would seem that we have thus far failed on both of these counts. Actually, we have little reason for saying that the measurement of ionization in a gram of air tells us very much about the ionization in a gram of tissue; and the work of the Memorial group definitely indicates that they are not the same. Dr. Ellinger in his earlier paper alluded to the fact that particular injury is produced in the lymphatic tissues of the goldfish, but I do not believe he can say definitely whether it was damage to these cells that caused death of the goldfish. Thus, not only are we unable to measure the ionization produced in the tissues, but we do not know in which tissues or cells we need to measure the radiation. This does not reflect on the quality of Dr. Ellinger's work but rather on the difficulties of the problem. Nor does it discredit the advantages pointed out by Dr. Ellinger for the use of goldfish for certain types of studies.

F. Ellinger, M.D. (*closing*): In answering Dr. Henshaw I want to say that I have shown that there is a latent period for the lethal action of roentgen rays. This makes it very probable that destruction of lymphatic tissue is responsible for the death of the fish. It is, of course, impossible to exclude with certainty the photochemical formation of toxic products. But if the latter is assumed to play the important rôle for the lethal effect, such a latent period is less probable. Furthermore, we found definite and extensive changes in the central nervous system, which could be responsible for the death of the fish. However, since the lymphatic tissue is known to be more radiosensitive, and since the latent period is in good agreement with facts observed in the destruction of lymphatic elements in other animals, I believe we may fairly well assume that destruction of lymphatic tissue is the cause of death in the fish. It may not be the only one, but certainly it is an important factor.

Dr. Henshaw pointed out that there is good reason to assume that ionization in air and in tissue may not always run parallel. This, in my opinion, makes it necessary to continue studies on the biological action of roentgen rays with as varied material as possible. This will broaden our knowledge about the mechanism underlying radiation therapy.

The Biological Effect of Roentgen Rays of Long and Short Wavelength on the Totally Irradiated Rat[1]

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THE PURPOSE OF this study was to compare the biological effects of three x-ray wavelengths on the totally irradiated rat. The lethal dose was used as the basis for comparison. At the same time, the result of irradiating the ovaries was studied by observing the fertility of the rats in the non-lethal experiments.

The biological effect of different wavelengths has been investigated by Packard (1), using fruit fly eggs; by Quimby (2), with erythema doses on the skin; and by Harvey, Dresser, and Warren (3), who studied the sterilizing effect of different wavelengths on rabbit tumors. In general, all found the effects of different wavelengths to be the same. In none of these studies, however, with the possible exception of the work of Harvey, Dresser, and Warren on testicular tumors, was penetration a factor. In irradiation of the whole rat penetration becomes a factor, and the findings in this paper therefore add new observations.

Whole rats were irradiated with heavily filtered rays at 400 kv., lightly filtered rays at 100 kv., and unfiltered rays at 100 kv. The doses were increased in different groups of rats 200 r units at a time until death resulted. Animals not destroyed were mated after five weeks to observe the effect on fertility. The rats were virgin females about two months old, each weighing approximately 150 gm. This study was continued over a period of eight years and nearly 500 rats were irradiated. The results obtained with the last 49 consecutive animals have been tabulated.

The x-rays were generated by two machines. One was a 100-kv. generator with single valve rectification; the other was a 400-kv. machine with full-rectification, Villard circuit and Thoraeus A filter (0.6 mm. Sn + 1.5 mm. Cu + 1.0 mm. Al). The target skin distance was 80 cm. in all. An effort was made to keep the time of irradiation the same for the different wavelengths. The r units were measured in air by means of a Victoreen r meter.

With filtered radiation an entrance dose of 800 r at both 100 kv. and 400 kv. caused death. The animals died in a few days of enteritis. With unfiltered radiation at 100 kv., a 1,200 r entrance dose caused death in a week, as above. With a 1,000 r entrance dose of unfiltered radiation the animals lost weight and died in two to four weeks. Fertility continued, with all wavelengths, up to a dose which caused death.

As the lethal entrance dose of unfiltered and filtered waves was not the same, the exit dose was determined to see if it offered a better means of comparison. This was computed by means of a paraffin phantom, 3.5 cm. thick, and a paper box, 3.5 cm. thick, in which 5 rats were tightly packed. At 400 kv. the exit measurement was three-fourths of the entrance measurement; at 100 kv, filtered, it was three-fourths of the entrance measurement; at 100 kv., unfiltered, it was half the entrance measurement.

The exit measurement which will kill all rats in a week is constant in the wavelengths studied. With a 500 r exit measurement at 100 kv., unfiltered, the animals die slowly, yet with a 600 r exit measurement the effect is uniformly lethal in all three wavelengths while the lethal entrance dose varies with filtered and unfiltered rays (Table I). Unfiltered radiation of long wavelengths is thus not as effective as filtered radiation in the destruction of

[1] From the Department of Obstetrics and Gynecology of the University of Rochester School of Medicine and Dentistry and the Strong Memorial Hospital. Accepted for publication in October 1940.

TABLE I: EFFECTS OF LONG AND SHORT WAVELENGTHS ON TOTALLY IRRADIATED RATS

Entrance Dose	100 Kv. Unfiltered	100 Kv. 0.25 Cu Filtration	400 Kv. Thoraeus A Filter	Exit Measurement
400 r	....	....	5 rats; 5 mated; 1 litter	...
600 r	5 rats; 5 mated; 0 young	4 rats; 3 mated; 0 young	5 rats; 5 mated; 1 litter	...
800 r	5 rats; 5 mated; 2 litters	....	....	...
800 r	....	4 rats; all dead in one week	10 rats; all dead in one week	600 r
1,000 r	6 rats; 5 dead (slow death)	....	....	500 r
1,200 r	5 rats; 5 dead in one week	....	....	600 r

rats, probably because of the high absorption rate in the superficial structures of a goodly part of the beam. In the extremes of useful filtered radiation with rats, any difference of effect is too small to be measured. The entrance dose cannot be used to compare the biological effect of unfiltered radiation with filtered radiation in an animal of some thickness where penetration is a factor. The exit measurements seem to be more valuable in this respect.

CONCLUSIONS

1. With the extremes of filtered radiation (100–400 kv.) used in this study the lethal entrance dose in the rat is the same.
2. Unfiltered x-rays (long waves) are not as lethal for rats as short waves when compared by entrance doses, but are equally so when compared by the exit measurements.
3. The castration dose is larger than the lethal dose in a totally irradiated rat.

Acknowledgments: I wish to thank Dr. Karl M. Wilson, Dr. George W. Corner, and Dr. Stafford L. Warren of the University of Rochester, School of Medicine and Dentistry, and Dr. Leslie Lingeman of the Rochester General Hospital, for making available the facilities for this investigation.

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Some Important Considerations of Soft Tissue Anatomy as Revealed by Radiography of Anatomical Cross-Sections[1]

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THE RECENT increase in interest in the radiographic exploration of the soft parts and the growing use of radiography in the teaching of anatomy have again focused attention on the study of soft-tissue anatomy by radiographic methods.

While it is quite true that the larger anatomical details of the soft tissues have been exhaustively explored, nevertheless many of the finer points remain obscure and may be studied with profit. This holds true not only from the morphological aspect but from the physiological. The latest advances in soft-tissue technic have produced radiographs revealing an extraordinary amount of detail. Accurate interpretation requires an intimate knowledge of the anatomical basis of these shadows. It is the purpose of this paper to direct attention to the possibilities afforded by a study of radiographs of anatomical cross-sections and longitudinal sections.

Fig. 1. Section through brain and neck. Note detail of cortex and brain stem. The relations of the deep neck muscles are well shown.

While the possibilities of differentiation of very fine anatomical detail are almost limitless, a consideration of the technical factors is necessary if maximum results are to be obtained.

In the preparation of the specimen two essential factors are (*a*) adequate dehydration and (*b*) accurate cutting of sections so that a uniform width is maintained. For ordinary purposes radiographs of routine cross-sections prepared for study in class give surprisingly good detail. For maximum detail, however, it is necessary to employ a technic involving prolonged dehydration. Accurate cutting of the sections is important because irregularities in width are readily detected, giving rise to asymmetry of anatomical detail in comparable areas. This may be overcome by embedding the body in paraffin, thus facilitating evenness of cut.

The x-ray technic employed is quite important. Best results are obtained using a high milliampere second ratio, 500–1,000, with a kilovoltage (peak) of 30. The tube distance is 6 feet and cardboard holders are used. No special emulsion is required.

For those who are interested in making radiographs of anatomical cross-sections to show the utmost detail, the technic for the preparation of the body as developed by Mr. H. O. Mahoney, of the General Electric X-Ray Corporation is given. With this method it is unnecessary to inject the vessels, because of the exceedingly high detail obtainable. In the cross-sections ordinarily obtainable in the average department of anatomy, the vessels are injected with an opaque media. This may, in some instances, obscure some fine detail but is not a controlling factor.

[1] Read before the Radiological Society of North America at the Twenty-sixth Annual Meeting, Cleveland, Ohio, Dec. 2–6, 1940.

1. Select a body of average size which is as free from pathology as possible, and as soon after death as possible.
2. Line the body up in the anatomical position. Pad the table so that there will not be too much pressure on the shoulders and buttocks.
3. Embalm with formalin only.
4. Hang the body up in the icebox. Be sure that it is not twisted out of anatomical position. Let it stay in this stage for three months so that the formalin will saturate and set the tissues.
5. Remove the body, amputate the arms at the shoulders, the thighs at the groin.
6. Place the torso in a wooden box especially made for the purpose, and fill with melted paraffin wax. The wax will adhere to, but will not be absorbed by the skin.
7. Let the torso stand in this stage for two, but not more than three days, lest the paraffin dry out and chip off. Embedding the body in a paraffin block makes it easier to handle during the sectioning, and makes it possible to obtain even sections.
8. The body is now ready to section. The transverse sections may be 1/2 inch in thickness, since they are small, easy to handle, and not likely to fall apart. The coronal and sagittal sections should be 3/4 inch in thickness.
9. As each section is cut, place it on a wire mesh of proper size, wash the section on both sides to remove foreign material, and then place it on a beaverboard or similar support. Once the sectioning is started it should be completed as soon as possible to prevent thawing.
10. The finished sections are now placed in the icebox for a period of four to six months for dehydration.
11. The sections are now ready to be radiographed.

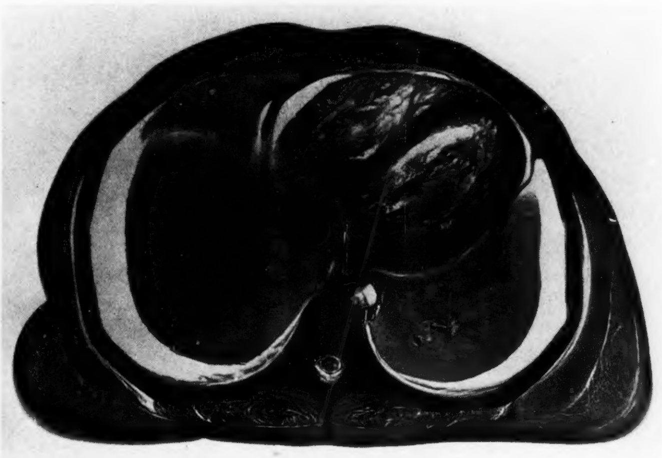

Fig. 2. Section through the heart. Note the detail of the cardiac musculature.

The soft tissues of the extremities may roughly be compared to a cylinder enclosing a dense structure, the bone. This cylinder has two totally enveloping membranes, which are circumferential. They in turn enclose groups of soft-tissue structures which tend to maintain a separate identity, *viz.* (*a*) muscles, (*b*) vessels, (*c*) nerves. Each of these groups has fascial coatings enclosing in turn other fascial envelopes. All of these fascial enclosures constitute a most remarkable and almost innumerable series of potential spaces.

They are, generally speaking, freely interconnecting, at least to air, and may be distended by air or exudates.

The space between the skin and superficial fascia consists of fascial pockets enclosing fatty tissue, running vertically, though in certain areas poorly defined horizontal fascial layers may be noted. The vertical pockets are not freely communicating with air but are distensible. The relation between depth of fatty tissue and muscles may be of significance in nutrition, especially in infants.

In radiographs of normal muscle in the living subject the outlines of the muscle groups are usually delineated, as are the subdivisions within the muscle group. The smaller divisions within a single muscle are more readily seen in the adult past middle age than in childhood. The smaller fascicular spaces are well delineated in the cross-sections. The superficial fascia may be seen to dip deep between the muscle groups, forming in part the major division of muscles. All of these form potential spaces but are distensible by air. Muscle atrophy tends to accentuate these divisions, particularly the smaller ones.

The nerves and vessels apparently have a similar system of enclosures which are distensible by air to a varying degree. The same may be said of the blood vessels. The relations of the potential fascial spaces of these three groups of structures are beautifully shown in cross-sections and to a lesser degree in longitudinal sections.

In radiographs of cross-sections of brain tissue the detail is extraordinary, and many of the tracts may be delineated, thus affording an excellent means of studying neural anatomy.

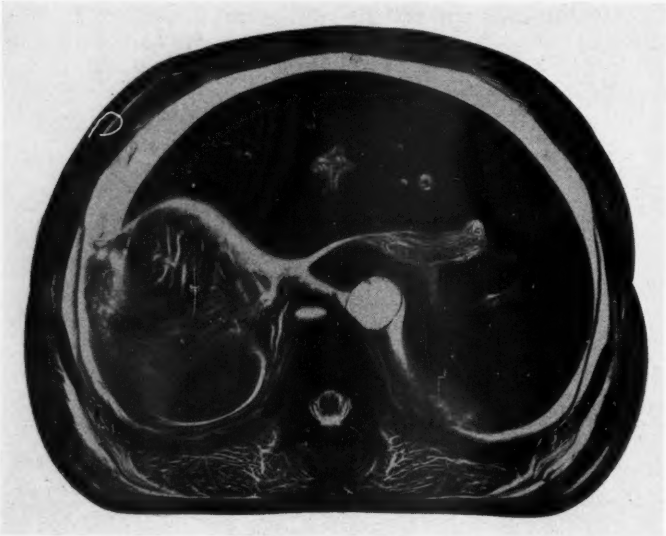

Fig. 3. Section through abdomen. The pancreas, spleen, and a portion of the stomach are shown. Note the relations.

In our estimation the increased detail obtainable by the radiograph is much more satisfactory for teaching purposes than the mere inspection of the sections and drawings made therefrom. If careful injection of the vessels is made, the relation of the vascular to other soft-tissue structures is made more striking.

CONCLUSIONS

1. Radiographs of anatomical cross-sections afford an excellent means of teaching anatomy to supplement dissection.

2. Study of these radiographs reveals

Fig. 4. Section through lower shoulder region. Note relation of the muscles to the scapula.

valuable information regarding some poorly understood aspects of soft-tissue anatomy.

3. Valuable information regarding the cross relationships of soft tissues may be obtained, which will be useful to the radiologist in interpretation of soft-tissue radiographs.

4. Mahoney's technic for the anatomical preparation of the sections is given.

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DISCUSSION

J. Robert Andrews, M.D. (Cleveland, Ohio): I think that as practising radiologists we can see a need for this sort of study. Several years ago I had an opportunity to work with the technic of body section roentgenography and found myself much confused by the fact that, while we are used to thinking of the roentgenogram as a picture of composite sections, still we are not used to thinking in terms of sections themselves.

We have, for example, very definite concepts as to what the floor of the middle cranial fossa looks like in the ordinary lateral roentgenogram of the skull, but it is a much different structure as seen from the side at different levels in true plain sections with a planigraphic technic. I should like to ask Dr. Carty about the immediate use of his study so far as this newer technic of body section roentgenography is concerned.

I should also like to ask the relative importance of the technic, so far as the factors employed in the x-ray examination are concerned, as compared to the preparation of the tissue. In other words, there is a difference in clarity between ordinary roentgenograms of normal tissues and those of his anatomic sections. That may be due simply to the thinness of the cut. I should like to know what rôle that plays.

In general it appears to me that there is an immediate need for this sort of study and we can find much practical value in the study of such anatomic sections.

John Russell Carty, M.D. (*closing*): The technic of processing the sections before radiography is most important if the utmost detail is to be obtained. Most of the radiographs which we showed were made from sections prepared and cut in the customary manner for students, and were somewhat shopworn. I deliberately selected these because it shows what can be done without a great deal of trouble. While excellent results can be obtained by using sections which have not had special preparation, for the utmost detail the technic here desoribed is superior.

Dr. Andrews' reference to the use of the sections in connection with laminagraphy is very well taken. When he views a radiograph, the experienced observer attempts to orient himself in terms of three dimensions, although the radiograph may represent a single plane. I have found that the study of these cross-sections is a valuable aid in acquiring a mental projection of depth. This is rather difficult to describe, but is quite helpful in interpretation. From the strict anatomical aspect the actual relation of one muscle group, for instance, to another, is of course important, but I do think that the sense or feeling of depth is obtained more readily by a study of these sections.

I wish to take this opportunity to express my appreciation for the interest and cooperation shown by Dr. Joseph C. Hinsey, Professor of Anatomy, Cornell University Medical College.

Rectal Dyschezia: A Misnomer for Megarectum[1]

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FOR SOME YEARS past, textbooks of radiology and medicine have included brief mention of an entity known as "rectal dyschezia." Usually the subject is dismissed very briefly, and comments on the etiology are vague. Illustrations accompanying the discussions often picture a dilated rectum, the dilatation sometimes encroaching upon the rectosigmoid. The condition is set down as due to decreased irritability of the rectum and to diminution of the impulse to defecate, with a consequent accumulation of feces in the rectal ampulla.

Several features of such a case recently coming under our observation prompted us to investigate the subject of "dyschezia" more thoroughly, and the ineptness—or we might say obsolescence—of the term was impressed upon us as we probed for diagnostic criteria or illuminating notes on etiology.

CASE REPORT

C. B., housewife, twenty-seven years of age, had experienced difficulty in emptying her bowels since childhood. Fecal accumulations at that time had given her so much distress that her father had repeatedly cleaned out the scybalous masses digitally. Later she came to depend upon enemas, but found them increasingly inefficient. She could introduce the enema solution, fill the colon, and evacuate the solution, but the increasing abdominal mass would be unaffected.

The patient first came under observation with an acute abdominal attack, diagnosed as appendicitis. At operation the pelvis was found filled by a huge, dilated segment of bowel. Following the operation, a fecal accumulation was removed by a series of enemas.

The patient was next seen for pregnancy, and a fecal mass had to be dealt with as before. At the time of delivery there was a reaccumulation of feces, despite which a normal delivery was effected. Following delivery, colonic flushings were resumed by the patient but she later sought advice because of the return of the pelvic mass.

A barium enema was given, and the accompanying illustrations reveal the picture which was presented. At first it seemed impossible to introduce the barium; then a faint trickle of the suspension was seen surrounding a mass which completely filled the rectal ampulla. When the colon had been filled, barium entirely obscured the underlying mass. The roentgen diagnosis was a huge scybalum filling a greatly dilated rectum. This was confirmed clinically when, by a series of enemas, the fecal accumulation was gradually broken up and evacuated, with disappearance of the mass.

This patient had no evidence of any rectal stricture or atresia, and the fact that during her childhood her father had been able manually to remove fecal impactions would seem evidence that she had no atresia then.

A review of the literature on "congenital idiopathic dilatation of the colon" reveals an interesting change in trend of thought so far as etiology is concerned. Earlier stress was laid chiefly on strictures and atresia as the cause of proximal dilatation—a logical sort of cause-and-effect reasoning, but one which has received little clinical support. The later literature, mostly by virtue of the excellent contributions of the neurosurgeons, deals with megacolon from the standpoint of its anomalous nerve supply.

The first example of congenital idiopathic dilatation of the colon was probably reported by Charles Michel Billard, in Paris, in 1828 (1). Other cases were reported by Ebers (1836), von Ammen (1842), Oulmont (1843), Banks, Banfer, Favelli (1846), Little and Galloway (1850), Gay (1854), Henoch (1861), Levitt of Chicago (1867)—this last the first American case—and others. In 1886 Harald Hirschsprung reported two cases with constipation, distention, and dilatation and hypertrophy of the colon (2).

Some of the anatomical considerations upon which the present concept of megacolon is based may be briefly reviewed as follows:

The sympathetic nerves which cause relaxation of the intestinal musculature

[1] From the Departments of Radiology and Medicine, West Suburban Hospital. Accepted for publication in August 1940.

Figs. 1 and 2. Megarectum: Appearance after administration of barium enema (left) and following partial evacuation of the enema (right). In Fig. 2 (right) a huge scybalum is seen occupying the rectum.

and increased sphincteric tone originate in the anterolateral columns of the spinal cord. The preganglionic fibers pass through the first and second lumbar ganglia to the inferior mesenteric plexus. There they join trunks from the celiac plexus, semilunar, and aortico-renal ganglia, forming the inter-mesenteric plexus. The inferior mesenteric nerves are formed mostly of postganglionic fibers (3).

The rectal sympathetic nerves are found in the presacral nerve of Latarjet, the lateral roots of which arise from the first to fourth lumbar ganglia while the middle root is a continuation downward of the inter-mesenteric plexus. In the pelvis this complex nerve divides into two hypogastric nerves joining the hypogastric ganglion, from which the postganglionic fibers pass to the lower rectum, the internal sphincter of the anus, and pelvic viscera (15).

The parasympathetic, which acts in opposition to the sympathetic, *i.e.*, relaxes the sphincter and increases muscle tone and peristalsis, has its origin in sacral outflow. These fibers, preganglionic, pass through the pelvic plexus of each side as two nerve bundles on the hypogastric plexus (16).

Robertson and Kernohan (18) sum up the situation admirably:

"For, in this affliction, as in cardiospasm, judging from our experience, there is no obstruction or spasm to account for the increase in size of lumen. Apparently there is a simple failure of peristaltic activity. The smooth muscle can contract and stretch and even hypertrophy, but the propulsive mechanisms remain the same.

"Our microscopic study of the colon (in this case) consisting of examination of paraffin sections stained with hematoxylin and eosin, Gros-Bielschowsky silver impregnation, and cresyl violet, confirms this suspicion. The cells and fibers of the plexus of Auerbach are definitely smaller than normal, vacuolated, and the ganglion cells are absent or very imperfectly formed. The same appearance was noted in sev-

eral other cases of Hirschsprung's disease. . . . . So-called idiopathic dilatation of ureters, renal pelves, gallbladders, bile ducts, and stomachs, and many other abnormalities might reveal a pathologic complex similar to that which we assume is present in the diseased colon and oesophagus. It is by no means impossible that the lesion in so-called paralytic ileus of the small intestine so frequently associated with peritonitis may be explained by toxic changes in the myenteric plexus."

By a consideration of all these etiologic factors, it is suggested that the term "rectal dyschezia" be abandoned and that the condition so designated be referred to as "megarectum."

The results of sympathectomy in selected cases would seem to bear out the reasoning of the neurosurgeons as to etiology (4, 6, 7, 15, 17, 20, 22, 24, 30). We say "selected" because the element of duration must be considered. In long-standing cases such changes take place in the bowel wall that it can no longer respond to a readjustment of its innervation. The two best methods for determining this response before operation have been the use of spinal anesthesia and of parasympathetic drugs (8, 11, 19, 13, 26).

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Parasternal Diaphragmatic Hernia with Report of a Case on the Right Side[1]

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Although a rapidly increasing number of cases of diaphragmatic hernia have been recorded, the publication of the following report seems to be justified as the hernia in this instance belongs to an infrequent group and presents, besides the classical symptomatology, some unusual features. According to the available literature, this is the only reported case of right-sided parasternal diaphragmatic hernia with an acquired total atelectasis of the middle lobe of the right lung. This is of importance because of the light thus thrown on the etiology of the condition.

EMBRYOLOGY AND ANATOMY

Before discussing the general aspects of our case it seems advisable to give a short review of the embryology of the diaphragm and of its anatomy, especially in relation to this example. In the embryo of about two weeks there is a common body cavity. A primitive diaphragm, lacking any muscle element, is formed by the fusion of the anteriorly and ventrally situated *transverse septum*, the dorso-lateral *pleuro-pericardial membranes*, and parts of the *pleuroperitoneal membranes* (Broman, 1, 2; Gruber, 14; Hedblom, 18). The muscular component is of later and separate origin. Therefore, the presence or the absence of a sac and its histologic composition will, at least to some extent, indicate the time of formation of a congenital hernia. For the formation of a congenital diaphragmatic hernia after the twelfth embryonic week, according to Werthschützky (39), the pressure changes brought about by the underdevelopment of a pulmonary lobe seem to play a part. Weakness of the connective tissue of the diaphragm is a prerequisite for this process and also plays an important rôle in the formation of those herniae which are acquired in extra-uterine life (Schwalbe, quoted by Gruber, 14).

As a general review of the anatomy of the diaphragm exceeds the scope of this paper, we shall refer to it only in so far as it is essential for the understanding of our case. The *parasternal space, Larrey's space*, or *foramen of Morgagni* (27) is a bilateral retrosternal muscle-free triangle covered by peritoneum on the undersurface and by pericardium above. It is limited anteriorly by the sternum, medially by the sternal portion and laterally by the costal portion of the diaphragm. The latter, in this region, is attached to the cartilage of the seventh rib. Through this space pass the terminal branches of the internal mammary vessels.

CLASSIFICATION

Classification of diaphragmatic herniae is somewhat difficult and greatly confused. A recent discussion of the different forms of classifications will be found in a paper by von Greyerz (13). In spite of the fact that the following classification is somewhat old-fashioned and in view of modern conceptions of anatomy slightly incorrect—since a hernia without a sac is no hernia but a prolapse according to Gruber (14), von Meyenburg (26), and Sigmund (33)—it has the great advantage of being by far the clearest and simplest. It is used by Eppinger (8, 9), Hedblom (18), Hitzenberger (20), and other authorities. According to it, diaphragmatic herniae are divided into the following groups:

(1) Congenital: present at birth. Absence or presence of a sac and its composition indicate the time of malformation; generally *no sac* is present.

(2) Acquired: Developing after birth in

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a congenitally weak area such as Larrey's space. These generally *have a sac.*

(3) Traumatic: Due to penetrating injury of the diaphragm. These generally have *no sac.*

Each of these groups is further subdivided into true and false. Eventrations are not included in this classification.

CASE REPORT[2]

Clinical History: The early history in this case seems to be devoid of any incidents which

Fig. 1. Roentgenogram (Oct. 14, 1926) showing herniation of the right diaphragm with considerable displacement of the heart toward the left. There is also an atelectatic condition of the right mid lobe area, with an isolated Ghon's node near its periphery.

might be referred to a parasternal hernia. At the age of forty-one the patient suffered from right abdominal pain. Appendectomy revealed a normal appendix. As the pain persisted, a few months later a cholecystectomy was done and stones were found. The operation was followed by continuing pain, which was attributed to a traumatic neuritis of the right arm. At the age of 57 years the patient underwent an operation for a femoral hernia. A few years later she began to have bronchitis with marked dyspnea and cardiac insufficiency. At this time (1922) the first x-ray examination of the chest was made, revealing a peculiar shadow in the right lung field. No definite diagnosis was made but the possibility of a neoplasm was considered in the beginning. In the following terminal fifteen years of the patient's life the x-ray findings remained essentially the same. From one of the early films a roentgenologist suggested an encapsulated interlobar effusion and advocated paracentesis. This, however, was not performed. A diagnosis was never established. At no time was barium contrast medium given as an aid to x-ray examination.

The patient suffered from hypertensive cardiovascular disease and her blood pressure reached the peak of 200/90 in 1930, when she was 69 years old. Despite slowly increasing myocardial insufficiency, she was ambulant up to ten days before her death. She had persistent tachycardia due to auricular flutter, which developed four months before death and did not respond to medication. The pulse was always between 140 and 160. There were, however, no subjective symptoms. The terminal illness, lasting three days, was characterized by falling blood pressure, edema of the legs, congestion and edema of the lungs. Death occurred August 7, 1938, at the age of 77, and a limited necropsy was performed on the same day.

Necropsy: The significant findings at necropsy on the stout, obese woman were as follows: The diaphragm was at the level of the fifth rib on either side. Behind the lower border of the sternum, at the level of the junction of the cartilage of the seventh rib to the sternum, slightly to the right of the mid-line, was an approximately round hole, 5 cm. in diameter, on the under surface of the diaphragm, the edges of which were smooth. The localization of this hole corresponded to the place where the right space of Larrey is normally found. A definite description is, however, somewhat difficult as the normal anatomical borders, which consist of muscle, had been replaced by fat and connective tissue. The terminal branches of the right internal mammary vessels, however, passed through the hole and therefore make it likely that it corresponded to the right space of Larrey.

The hole just described was the orifice of a hernial sac which extended upward, outward, and slightly posteriorly, into the right thoracic cavity, reaching the level of the third rib anteriorly. Its neck consisted of firm connective tissue without muscle fibers. The sac was entirely covered by serosa. Its anterior wall was formed by rather loose connective tissue which was rich in blood vessels, the dome and the posterior wall by the tendinous portion of the diaphragm. Its inner surface was lined by peritoneum.

In this hernia a loop of transverse colon, part of the great omentum, and the upper part of the round ligament of the liver were found. The contents were easily removed; they were not adherent and showed no signs of vascular disturbance.

Most remarkable was the *middle lobe of the right lung,* which was reduced to a thin strip of tissue. It contained a calcified nodule, apparently a healed primary tuberculous focus. Its bronchus was of normal caliber but 1 cm. from its root it showed an upward kink and from this point on its lumen was collapsed. Microscopic examination revealed advanced atelectasis and fibrosis with much coal pig-

[2] Presented before the New York Pathological Society, April 27, 1939.

ment present. Corpora amylacea were found in some of the alveolar spaces. Elastic fibers were abundant and were also present in the collapsed alveolar walls. In places there were focal deposits of cholesterol crystals with a foreign-body reaction. The right lower lobe was slightly impressed by the hernia but was generally unaltered and not atelectatic. It showed evidence of the generalized chronic passive visceral congestion.

The hernia displaced the greatly enlarged heart (*cor bovinum*) to the left. The apex was in the anterior axillary line. There were signs of a healed mild adhesive pericarditis and considerable adipositas. The valvular apparatus was intact.

The anatomic diagnosis was true parasternal hernia on the right with displacement of the heart to the left; compression atelectasis of the middle lobe of the right lung.

PATHOLOGY OF PARASTERNAL HERNIA

The anatomy of the parasternal spaces has been discussed above. Theoretically the parasternal hernia may be either left-sided or right-sided, or in rare instances medial (Funck-Brentano, 11; Kratzeisen, 21), according to the anatomical localization of the hernial opening at the site of the left or right space of Larrey or between them. Many cases have been reported as right-sided or left-sided parasternal herniae which anatomically were actually mediastinal herniae, as the muscles which determine the anatomical limits had been destroyed and replaced by fat or connective tissue (Garraud and Bastien, 12; von Greyerz, 13; Kratzeisen, 21). In view of this, and since, furthermore, herniae which go through the left parasternal space may reach into the right pleural cavity and *vice versa* (Eppinger, 8 and 9; Kratzeisen, 21), and as the physical findings are different according to which pleural cavity is affected (Eppinger, 9), it seems to be advisable to classify parasternal herniae as right-sided or left-sided according to the pleural cavity into which they project and not according to the site of the anatomical localization of the orifice, which in many cases it is impossible to determine. Those herniae which do not extend into either pleural cavity should be called

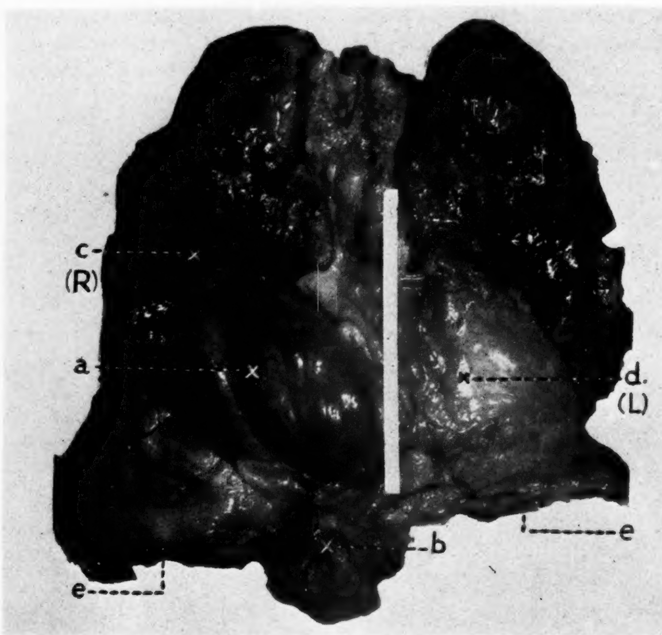

Fig. 2. *a*. Hernial sac. *b*. Orifice, with transverse colon protruding from it. *c*. Atelectatic middle lobe (R). *d*. Heart (L). *e*. Diaphragm.

mediastinal (Funck-Brentano, 11). Rare herniae which project into both pleural cavities are correctly called bilateral parasternal herniae (May, 24; Morton 28).

A hernial sac seems to be typical for the parasternal hernia. According to Hedblom (17, 18), all but three cases examined at operation or at necropsy had a sac. These three were in children.

The typical contents of the parasternal herniae are transverse colon and omentum, but other organs of the abdominal cavity have occasionally been found.

ANATOMICAL CHANGES BROUGHT ABOUT BY THE PARASTERNAL HERNIA

Herniae extending into the right pleural cavity displace the heart considerably to the left, as in our case, whereas those which go into the left pleural cavity displace the heart posteriorly and not to the right (Eppinger, 9). There may be compression of the phrenic or vagus nerve. Slight compression of the lower lobes of the respective lungs seems to be common. We were, however, unable to find a case in the available literature which showed a total acquired atelectasis as in the case presented. This, apparently, was due to compression and kinking of the main bronchus of the middle lobe of the right lung by the hernia (see below under "Theory of Formation of Parasternal Hernia").

COMPLICATIONS

Strangulation occurs, according to Morton (28), in 10 per cent of all parasternal herniae. Ellinger (7) and Eppinger (9) put the incidence of this serious accident as high as 15 per cent. Incarceration seems to be quite frequent.

THEORY OF FORMATION OF PARASTERNAL HERNIA

From the very first papers which appeared on non-traumatic parasternal herniae it has been emphasized that many findings point to the fact that such herniae are acquired during extra-uterine life and are not present at birth. In the newborn the *relatively large liver* protects the parasternal spaces from any protruding intestine (Broman, 1, 2; Thoma, 35). Furthermore, at this age the transverse colon, which is usually found in parasternal herniae, has such a short mesentery that it could not possibly protrude into the pleural cavity (Thoma, 35). Thoma also proves statistically that there is not only an absolute but also a *relative increase of the size of the parasternal spaces in the adult* as compared to that in the newborn child. *Deposit of abnormal amounts of fat* in the spaces of Larrey, which presses the muscles apart and following fat reduction leaves large holes through which herniae may protrude, has been mentioned by Cruveilhier (5), Bevilacqua (3), and others as predisposing to parasternal herniae. Garraud and Bastien (12) found a lipoma in one of their cases projecting from the foramen of Morgagni into the pleural cavity. Interesting, also, is Waelli's case (38), in a twenty-four-year-old man with a hernia containing only omentum while the transverse colon had come up as high as the xyphoid process. A further very strong indication that these parasternal herniae form during post-fetal life is found in the age of the patients. Almost all were adults, and most were past middle life. Those few cases found in children and proved by autopsy were not typical parasternal herniae through the spaces of Larrey but were due to congenital malformations. They had no sac.

Another fact suggesting that these herniae generally form gradually late in life is the *compression atelectasis* of the middle lobe of the right lung found in our case, which we consider as certainly acquired. Many elastic fibers were present in the alveolar walls. Also the abundant coal pigment as far outward as below the pleural surface of the atelectatic lung indicated that it had not been transported into this lung in retrograde fashion by the lymph stream, but rather that the patient must have been advanced in years, certainly past the twenties, when the lung became atelectatic. Further evidence that this atelectasis must have been acquired is

the sharp kink found in the main bronchus of the middle lobe of the right lung. This acquired atelectasis proves that the case does not fall into Werthschützky's (39) group of congenital herniae which form due to underdevelopment of a pulmonary lobe.

Predisposing to the formation of parasternal herniae are general weakness of connective tissue, tendency to formation of herniae (as in our case), obesity, constipation, and increased intra-abdominal pressure (as for instance in pregnancy).

the heart is not in the line of extension of the hernial sac.

CLINICAL SYMPTOMS

Many cases show no subjective clinical symptoms (Eppinger, 8, 9; Kratzeisen, 21, and others). In other cases symptoms appear comparatively late. The most frequent symptom is gallbladder trouble, probably due to irritation of the phrenic nerve (cases of Harrington, 15; Meade and Ravdin, 25; Eppinger, 9; and others). Symptoms of strangulation are present in 10 to 15 per cent of all cases of parasternal hernia (Hedblom, 17, 18; Morton, 28; Eppinger, 9; Ellinger, 7). Other symptoms are constipation (frequent); stomach trouble simulating ulcer, due to compression of the duodenum by the crossing limb of the colon (Curri, 6; Morton, 28); anemia and loss of weight (v. Greyerz, 13; Steuer, 34); pain in the cardiac region simulating angina pectoris; shortness of breath; irritative cough. This enumeration is by no means complete and

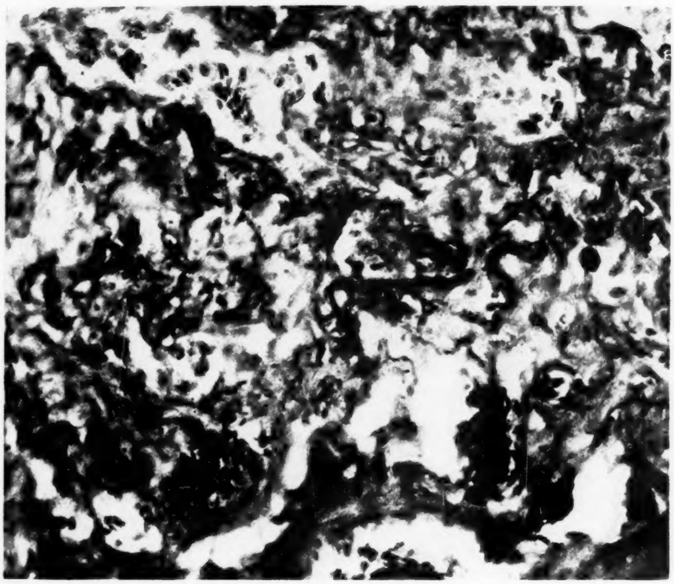

Fig. 3. Section of atelectatic lung (elastic tissue stain) showing anthracotic pigment and elastic fibers in the alveolar walls.

INCIDENCE

According to Morton (28), writing in February 1939, there are 120 cases of parasternal herniae known in the literature (incomplete bibliography). Funck-Brentano (11) in 1933 reported 58 cases (no bibliography) and Hedblom (18) in 1930 listed 48 non-traumatic cases, of which 27 were on the right and 21 on the left side (extensive bibliography). There seems to be a slight excess of right-sided herniae, apparently due to the fact that in such cases

serves only to indicate how many diagnostic pitfalls there are.

Eppinger (9) considers a succussion sound synchronous with the heart action to be diagnostic. There is generally tympany over the hernia on percussion, varying in intensity. In right-sided herniae there is considerable displacement of the heart to the left.

ROENTGEN FINDINGS

While formerly it was generally the exclusive privilege of the pathologist to discuss these cases, the number of parasternal herniae which have been diagnosed roentgenologically is increasing rapidly. The first of these was reported by Waelli (38) in 1912. Sielmann (32) was the first to use pneumoperitoneum in a parasternal hernia to ascertain whether a sac and adhesions were present.

The diagnostic appearances may be listed as follows:

1. A honeycomb-like area above the diaphragm, less opaque than the adjoining lung field, is found, if the gas-filled colon is in the hernia (Sielmann, 32). The haustration of the gut is often visible.
2. A rounded shadow, free from the lung and continuous with the diaphragm, seems to be diagnostic if omentum (Meade and Ravdin 25), or gut, filled with feces, is in the hernia.
3. Barium should be given in every case in which a diaphragmatic hernia is suspected in order to ascertain the diagnosis. In cases where only the omentum is in the hernia, this will, of course, be of little value (Meade and Ravdin, 25), but dislocation and fixation of the colon may give a hint (Waelli, 38).
4. Paradoxical movement of the diaphragm is said by May (24), Sielmann (32), and others to differentiate a hernia from eventration. This diagnostic sign, however, does not seem to be very reliable (Hayer, 16; Ruscioni, 29).
5. Pneumoperitoneum was used by Sielmann (32) to differentiate true from false parasternal herniae and to determine whether or not adhesions were present. Hayer (16) recommends this procedure but warns of its dangers, while Ruscioni (29) denies its value.
6. Differential diagnosis may frequently be rather difficult. A mediastinal or intrapulmonary "tumor" may be simulated. In Ellinger's (7) case, as well as in our own, interlobar fluid was suggested by the findings on the flat plate and paracentesis was advocated. If performed, this probably would have been fatal.

TREATMENT OF PARASTERNAL HERNIA

Because of the high incidence of strangulation (10–15 per cent), cases of parasternal herniae should be operated upon if there are no strict contraindications. The operative approach may be abdominal, thoracic, or combined abdomino-thoracic. The abdominal approach is advocated by Harrington (15), Hedblom (18, 19), Morton, (28) and Woolsey (40). Truesdale (37) prefers the thoracic approach if adhesions are present and considers x-ray examination of great assistance in their determination. Sauerbruch (30, 31) is opposed to the abdominal route as "a hernia of long standing may be adherent to vital structures, as the heart and lung, and the separation of such adhesions except under direct vision is fraught with danger." The combined route may be undertaken if it is impossible to free the hernia from one approach. Morton (28) prefers the latter procedure if adhesions are present.

SUMMARY

A case of right-sided parasternal diaphragmatic hernia, found at necropsy on a seventy-seven-year-old woman, is reported, and parasternal diaphragmatic hernia is discussed in general and with special reference to this case.

It is believed that this parasternal diaphragmatic hernia developed during adult life for the following reasons:

1. The patient falls in a group whose age and constitution are generally considered to predispose to parasternal hernia.
2. The clinical symptoms referable to

the hernia did not manifest themselves until the patient was middle-aged.

3. The many elastic fibers in the alveolar walls of the atelectatic portion of the lung prove that this compression atelectasis developed in extra-uterine life.

4. The abundant coal pigment in the atelectatic lobe shows that this condition must have been acquired rather late in life.

This case, since it fits in every respect into the classical picture of parasternal diaphragmatic hernia, and as the approximate time of onset is clear, lends strong support to the theory that such a hernia is acquired in extra uterine life.

For the clinical information on this case the author is indebted to Dr. Herbert G. Wiener.

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* Papers marked with an asterisk contain x-ray pictures of parasternal diaphragmatic herniae.

A Portable Dark Room for Processing X-ray Films Rapidly[1]

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SOME SURGICAL procedures may be more accurately controlled, and their duration may be shortened, by the aid of radiographic examinations during operation. The apparatus to be described here was devised to expedite development of x-ray films in the operating room.

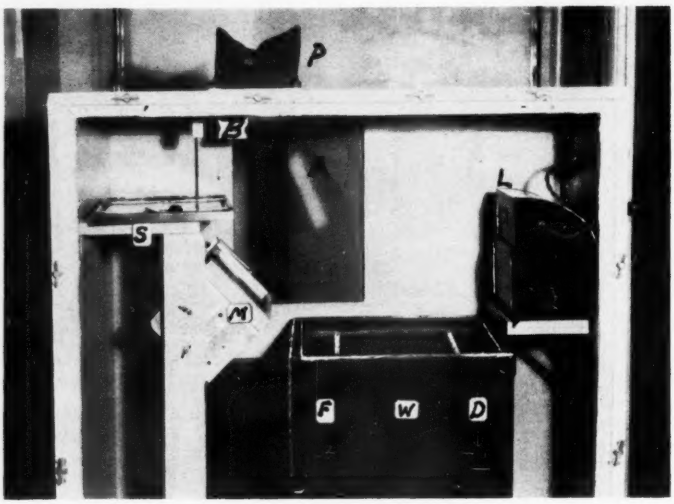

Fig. 1. Apparatus with curtain removed to show interior. P. Light shield for face of operator. B. Handle for light-proof door, which is opened only when operator's face blocks light in shield. A. Door for passing films into box. S. Shelf to hold cassette. M. Mirror. L. Safe-light. F, W, D. Tank for fixer, wash water, and developer.

The apparatus consists of a light-proof box enclosing a safe-light and tanks for processing solutions, so arranged that the film may be viewed during its development by use of a periscope and mirror which reflects rays transmitted through the film from the safe-light. The periscope has a flexible shield for the face, which excludes light from the apparatus but permits the technician to look into the interior of the box and watch the developing film as its image is projected onto a mirror. Manipulation of the film is made possible by the use of elastic ports into which the operator's arms are inserted, and the film may be removed from the developing solution at any desired stage. The entire apparatus is mounted upon a mobile base and may be wheeled into the operating room and used under bright lights.

A search of the records of the U. S. Patent Office shows that several pieces of apparatus have been devised for portable use in lighted rooms, but none of these has the features of an enclosed safe-light in the box or a reflecting mirror, making good visual control of development possible.

The inspiration for the design and construction of this device was primarily the need for such an apparatus to aid the surgeon in operations for internal fixation of

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fractures of the upper end of the femur. When several films are made during the course of any surgical operation, and further surgical procedure depends upon the radiographic findings, it is important that the films be quickly processed and made available to inspection with a minimum loss of time. This apparatus permits inspection of films in the operating room by the surgeon within two minutes after exposure, an interval which has been found quite satisfactory.

The intensity of the x-ray exposure is two or three times that which would ordinarily be used for a part of corresponding thickness. The temperature of the processing solutions is maintained between 72 and 75 degrees to hasten action of the developer. At higher temperatures there is a tendency for films to fog and the emulsion becomes too soft. Commercial developer is used.

The apparatus is shown in Figures 1 and 2. The cassette holding the exposed film is placed on shelf S (Fig. 1) and door A is closed. The technician, with both arms thrust through apertures in the curtain, can now safely open the cassette. The film is placed in the developing tank, D. The technician presses his face tightly into the rubber shield, P, of the periscope and opens a light-proof trap door, B, with his left hand. Now he can look into the mirror, M, and watch development by raising the film with his right hand so that rays from the safe-light, L, are transmitted through it to the mirror. The film is removed at the correct stage of development, transferred to the fixing solution for a short interval, then quickly rinsed and placed wet upon a window of the operating room.

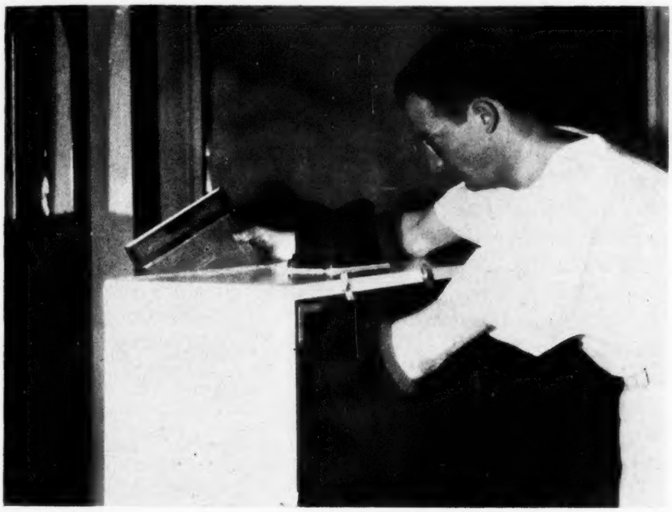

Fig. 2. Apparatus with curtain in place, showing method of passing the cassette into the box. The operator will watch the developing film through the light shield on top of the box.

Films developed in this manner are not perfectly processed films, but they are good enough so that the surgeon may obtain from them the information he needs. When several films are needed during an operation, the aggregate of time saved to the patient on the operating table is of much more importance than the slight loss of quality of the films.

Ollerenshaw (1) used a portable device consisting of a light-tight box with sleeves to permit manipulation of films in the box, but with his apparatus there was no way in which development could be visualized.

He used a single solution combining fixer with developer. This solution, however, is not stable and must be freshly prepared. Film was ready for inspection after it had been in the solution one minute. This is about the length of time required with our method, as we consistently place films on the operating room window for inspection within two minutes after the x-ray exposure. This time includes handling of the film before and after development as well as that which is required in the solutions.

Wilkinson (2) used Ollerenshaw's solution and found that about two minutes was required for development. He modified the solution by adding elon (metol), which hastens development, and claimed forty-five seconds as the developing time for this solution. It was used at room temperature, as difficulty was encountered with the emulsion when the solution was warm. Wilkinson did not mention use of a portable developing box.

Lönnerblad (3) tried a strongly alkaline solution of pyrokatechin, but it oxidized so rapidly that he had to develop the film in an air-tight glass container of small capacity that he could hold up before a safe-light in the dark room.

The single solution method used by Ollerenshaw and Wilkinson eliminates a separate process of fixation. We tried similar solutions and found the finished film to be of poorer quality than obtained by our method using two solutions of regular commercial developer and fixer. With the single solutions the fixation was incomplete and the films tended to darken while being viewed on the window. This disadvantage we believe outweighs the advantage of a single solution, especially as there is no practical difference in time between the two methods. With our two-solution method the films are good enough to be retained in the permanent files of the case as a record of the operation. In addition, the use of stable commercial solutions is simpler than a specially prepared solution for each case.

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A Study of Secondary Screening[1]

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Among the auxiliary means available to modern radiologists, great importance must be ascribed to the secondary diaphragm. Without this it would in most cases be impossible to obtain pictures sufficiently rich in contrast. It appears to be of interest, therefore, to endeavor to determine just what factors are decisive for the usefulness of this device.

With an object of average thickness, the diffuse radiation accounts for a large portion of the total intensity which influences the film or fluoroscopic screen. For example, at 70 kv. peak, with an object of about 10 inches in thickness, the secondary radiation constitutes about 90 per cent of the total intensity. Since this diffuse radiation causes a practically uniform fog on the film or screen if a diaphragm is not used, contrast is obviously greatly impaired.

The two types of Bucky diaphragm which are most commonly used are the Potter-Bucky diaphragm with a comparatively coarse grid and the Lysholm-Bucky diaphragm with a fine grid. The former, by reason of its coarse grid, must be kept in motion during the exposure. On account of the mechanism required for imparting movement to the grid, the diaphragm is heavy; it is difficult to locate in various positions and it is not suitable for fluoroscopy.

In order to eliminate the drawbacks of the Potter-Bucky diaphragm, Lysholm evolved, in 1926, a practical application of the so-called fine-grid diaphragm, which had been invented and patented by Bucky in 1922. This diaphragm differs from the Potter-Bucky diaphragm in that the thickness and the height of the lead strips have been reduced to such an extent that their shadows scarcely interfere with the picture. This diaphragm, therefore, can be kept stationary; the reduced dimensions render it more manageable, and it produces a sharper picture, since the distance between the patient and the film can be reduced.

In our endeavor further to improve the secondary diaphragm we have proceeded from the assumption that four principal features should be expected from such a diaphragm: (1) a high Bucky effect, that is to say secondary screening ability; (2) low absorption of primary radiation; (3) absence of interfering shadows due to the diaphragm; (4) minimum thickness, that is to say the least possible distance between patient and film.

The decisive factors for secondary screening capacity are primarily the height and the thickness of the absorbing strips. By reducing the thickness of the intermediate layer between the lead strips or by increasing the height of the diaphragm, a smaller free angle is obtained through which the radiation may pass. With reduction in the thickness of the intermediate layer, however, there is an increased absorption also of the primary radiation and, furthermore, the shadows of the lead strips become too wide, relatively, to the free intermediate spaces. If the height of the strips is increased, an even greater shadow is produced toward the border of the picture. By experiments we have established the height, width, and distance between the strips which will provide a maximum of secondary screening with the least possible absorption and the least possible amount of shadow due to the strips themselves; that is to say, these three factors have been adapted as favorably as possible relative to one another.

It must not be forgotten, however, that diffuse radiation emanates also from the lead strips of the diaphragm, partly second-

[1] Read before the Fifth International Congress of Radiology, Chicago, 1937.

ary rays produced by the focal radiation and partly tertiary rays produced by the secondary radiation from the object. Furthermore, there will be a diffraction and reflection of the radiation in the crystal grating in the outermost portions of the lead strips. For the purpose of absorbing this lead radiation, tests were made with intermediate layers of aluminum, magnesium, beryllium, and alloys with similar properties. A reduction of the intensity of the radiation from the lead could thus be brought about as a result of absorption in the light metal intermediate layers. In order altogether to eliminate the lead radiation, the lead strips are covered with a layer of tin, which entirely absorbs radiation from this source. The strips of tin are covered with a nickel or iron layer and this, in turn, is united with the intermediate layer of light metal, which consequently needs only to absorb the soft radiation emanating from the nickel or iron.

Through painstaking tests made with grid elements in fivefold enlargement, the improvement of the Bucky effect was established with certainty at about 10 per cent, due to the absorption of the secondary and tertiary radiation emanating from the lead strips.

A few words as to the method by which the Bucky effect was measured are appropriate at this point.

The experimental contrivance employed was evolved by Dr. Lindblom (Acta Radiologica, 1934). A water phantom, consisting of a cellon bowl having a bottom surface 10 × 10 in. and containing 10 inches of water, is placed above the diaphragm to be examined. Immediately beneath the diaphragm is the cassette with intensifying screens and the film. A 10-inch phantom was chosen, since with respect to diffuse radiation this phantom may be taken to correspond to an object of average thickness in the field of medical radiology. Intensifying screens have been used to provide for conditions approximating as closely as possible those which occur in practice. In all of the investigations the same cassette and the same intensifying screens have been used. The cassette is a normal metal cassette with a metal frame and a top plate of 1 mm. Al. Placed directly above the water phantom is a lead strip about 2 cm. wide, which screens off the primary radiation, so that the film is darkened only by the secondary radiation emanating from the object (water phantom). Finally, a piece of lead is placed on the cassette. The film beneath this, which is not exposed to any radiation, is used to determine the fogging caused in the development.

With each of 6 diaphragms 6 exposures of varying intensity were made and the films were observed for (*a*) the effect of primary radiation plus the diffuse radiation with different times of exposure, (*b*) for the effect of diffuse radiation alone with corresponding periods of exposure, and (*c*) for the "fog of development." If the darkening effect of the primary radiation minus the "fog of development," which we may call the basic darkening, is represented by S, and the darkening due to the scattered radiation minus the "fog of development," which we will call the secondary darkening, by S_s, then the darkening due to the primary radiation alone, S_p, must be equal to $S - S_s$. This value, S_p, may also be called the "contrast width" for the given exposure, since it represents the difference between the highest and the lowest darkening values.

The contrast between the two surfaces of a negative viewed in transmitted light may, as is well known, be expressed through the difference in darkening between these surfaces. As a measure of the darkening, S, the absorption of light passing through a film or a plate is used. This is generally expressed by the equation

$$S = \log \frac{I_0}{I_1} = \log I_0 - \log I_1$$

in which I_0 and I_1 designate the light intensity prior to and after passage through the absorbing portion of the film.

An increased contrast width signifies a higher Bucky effect, since the latter involves a heightened contrast in the pic-

ture. By increasing basic darkening the contrast width is increased within certain limits. Therefore, the Bucky effect of a diaphragm can be demonstrated either by a contrast curve in which the contrast width (primary darkening) is shown as a function of the basic darkening, or through the primary darkening (S_p) expressed in percentage of the basic darkening (S). For this purpose a basic darkening value of $S = 1.8$ has been chosen, as it may be regarded as corresponding to the highest basic darkening of an x-ray film normally occurring in radiologic practice.

The measurements of the darkening effect have been performed with a densimeter having a light density wedge giving an accuracy to within about 0.02 darkening units. This degree of accuracy may be accepted as entirely adequate to judge the diaphragms from a practical point of view, since according to Bronkhorst, darkening differences below 0.075 are of scarcely any significance in radiography.

In all investigations, the focus-film distance has been kept constant, at 30 inches; the voltage has been 70 kv. peak (4-valve apparatus). The following diaphragms have been examined: metal diaphragm; Potter-Bucky diaphragm of standard type; a standard Lysholm diaphragm with intermediate layers of pasteboard between the lead strips; copper foils 0.6, 0.4, and 0.3 mm. Metal foils of a higher atomic weight, as for instance copper, have, as will be seen, a certain secondary screening effect, but by reason of their high primary absorption they are unsuitable as secondary diaphragms.

Estimating the Bucky effect by the primary darkening expressed as a percentage of the basic darkening value of $S = 1.8$ the following values were obtained:

Metal diaphragm	60%
Potter-Bucky diaphragm	48%
Standard Lysholm diaphragm	44%
Copper foil 0.6 mm.	22%
Copper foil 0.4 mm.	19%
Copper foil 0.3 mm.	18%

It has been shown in the foregoing that the metal diaphragm imparts a considerably increased contrast to the x-ray picture, due to its high Bucky effect. This circumstance may also be utilized when, for example, movable organs are to be exposed, in such a manner that the voltage and consequently the x-ray effect are increased, with a consequent reduction of the time exposure. In spite of the increased secondary radiation caused by this increased voltage, just as good a contrast will be obtained with the metal grid as with a diaphragm of some other construction used at lower voltage. The absorption of primary radiation by the metal grid at 70 kv. is equivalent to only 0.1 inch aluminum.

In the new metal diaphragm, the dimensions of the strip and the distance separating them are selected in such a manner that the shadows of the grid in the x-ray picture can scarcely be distinguished with the naked eye. The diaphragm may thus be used stationary, and the necessity of a complicated and expensive motion mechanism is obviated.

Finally, the thickness of the diaphragm is only about 2 mm. or 0.08 inch, that is to say about half of the thickness of the ordinary Lysholm grid, by reason of which the distance between the patient and the film is greatly reduced, with a corresponding improvement in the sharpness of the picture.

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CASE REPORTS

Peptic Ulcer of the Greater Curvature of the Stomach[1]

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Lesions of the greater curvature of the stomach are so commonly neoplastic and benign ulcers are so extremely rare that a diagnosis of a benign ulcer by the roentgenologist, clinician, or surgeon, is never justified. The danger of such a diagnosis is well illustrated by a case presented by Sproull (1). The surgeon, his assistant, and the hospital pathologist all agreed that the lesion appeared to be benign and it was accordingly removed by a simple V-shaped incision. On microscopic examination, however, it was shown to be malignant, and two years later a large annular carcinoma was found at the site of the resection by the roentgenologist and later by the surgeon. It was inoperable at this time and the patient died shortly after the second operation.

Fig. 1. Case 1: Roentgenogram showing the constricted pyloric antrum and an ulcer crater on the greater curvature of the stomach near the pylorus.

Matthews (2), in presenting two original cases in 1935, reviewed the literature and collected 4,603 examples of peptic ulcer. Of these, 139 or 3.0 per cent were found on the greater curvature, but as none of them was studied histologically, the real percentage of benign ulcers is not known. Matthews found 22 cases reported specifically, of which 10 were proved histologically. Three were diagnosed roentgenologically, without operation or autopsy. Nine were operated upon and studied grossly but no record of histological examination is given. Both of Matthews' own cases were on the greater curvature and were proved histologically. The ulcer was 12 cm. from the pylorus in one instance and 14 cm. in the other. Van Buchem (3) reported the only additional case in the literature in 1938, bringing the total to 13 proved cases.

Fig. 2. Case 2: Photograph of the opened stomach at autopsy. The large ulcer crater, about 4 cm. in diameter, is held open by the wooden applicator.

At the San Francisco Hospital in the last two years, two benign ulcers of the greater curvature of the stomach were found at autopsy. These are the only two examples in the hospital records.

CASE 1: I. S., a white female, aged 74, was admitted April 19, 1938, complaining of pain and stiffness in the left foot of three months' duration. One week after entry she had a severe attack of vomiting and complained of dull pain in the left upper quadrant. The vomitus was dark in color and the stool subsequently showed occult blood, four plus. No complaint referable to the digestive tract either before or after this episode, lasting only one day, could be elicited. Gastric analysis showed no free hydrochloric acid.

Roentgen examination (Fig. 1) following this attack revealed a lesion of the prepylorus with ulceration and a marked degree of pylorospasm, producing a large six-hour gastric residue. A diagnosis of carcinoma with ulceration was made. Repeated examination following a dietary régime showed no alteration in the appearance of the lesion and no change in the emptying time of the stomach.

[1] Accepted for publication in March 1941.

Operation was advised but was refused by the patient. On the morning of July 3 she was found in a condition of extreme shock and died a few hours later.

Autopsy: The stomach was dilated and contained about 400 c.c. of dark fluid. On the greater curvature of the prepylorus, about 0.5 cm. from the pylorus, was a round ulcer, 1.5 cm. in diameter. This was deep but had not eroded through the wall.

Histological examination (Fig. 3) showed an abrupt transition from the normal to a complete absence of mucous membrane. The surface was covered with fibrin, red blood cells, and a few polymorphonuclear cells. The area surrounding the ulcer showed some round cell infiltration in the submucosa. No evidence of malignancy was present.

Fig. 3. Case 1: Photomicrograph of ulcer, showing deep penetration at the margin.

Fig. 4. Case 2: Section through edge of ulcer. Note abrupt erosion of normal mucosa.

CASE 2: R. L., white male, aged 58, was admitted on June 15, 1938, in a semi-comatose condition, irrational, and not co-operative. Three days earlier he was seen by a physician, at which time he was vomiting blood. No additional history could be obtained. Death occurred on the second day following admission. No laboratory or roentgen examination was attempted.

Autopsy revealed a large ulcer, 4 cm. in diameter, 6 cm. from the pylorus, with smooth undermined edges, astride the greater curvature and extending posteriorly to the pancreas (Fig. 2). The edge of the ulcer was thin and the mucosa normal up to the edge.

The base of the ulcer was shown histologically to be formed by dense young fibrous tissue infiltrated by lymphocytes. The lesion extended almost to the serosa. No evidence of malignancy was seen (Fig. 4).

The sections of these two cases were reviewed by J. L. Carr, M.D., and G. Y. Rusk, M.D., clinical pathologists, both of whom corroborated the original diagnosis of benign ulcer.

SUMMARY

A review of the literature and two original cases of benign ulcer of the greater curvature of the stomach are presented. Both cases are proved histologically. The microscopic sections of each were studied independently by two pathologists, who concurred in the diagnosis.

The percentage of such lesions compared to the total of all gastric ulcers is not known but it is extremely small. Only fifteen proved cases are known.

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Diagnostic Problems in Cases of Large or Giant Duodenal Ulcer[1]

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The roentgen diagnosis of gastro-intestinal lesions has advanced steadily since Cannon, in 1898, first made use of the opaque meal. Wider and more extensive use of x-rays with resultant wider experience, diffusion of information through the literature, and improvements in equipment have led to diagnostic refinements. Whereas mistakes were formerly due in large part to faulty technic, they are now chiefly attributable to errors in interpretation, provided the examinations and films are made in well equipped laboratories. Hypersthenic, obese, and very ill patients, however, still present difficult technical problems.

The object of this communication is to point out one of the diagnostic pitfalls that may be avoided, if we know of the existence of giant ulcers and are alert to their appearance. Errors of interpretation are not uncommon, especially in the diagnosis of gastro-intestinal lesions, but these cases do not always find their way into print. It is a common experience for the gastro-intestinal surgeon and the pathologist to be asked by the general practitioner as to the benignity or malignancy of a lesion and to have to reply that it is impossible to say from inspection and palpation alone, that opinion must be reserved until microscopic sections are available. The roentgen findings are likewise morphologic rather than microscopic. This is not an adverse criticism. It is a well known fact that a final decision must often be reserved. A working hypothesis is, however, necessary and here experience and clinical judgment enter. In the case to be recorded the error was due to lack of experience with the type of lesion eventually discovered. The case is of interest because of the paradoxical findings, because of their rarity, and because of the size of the pathological specimen.

Duodenal ulcers vary for the most part between 4 mm. and 10 mm. in diameter. It is unusual to find one exceeding a centimeter, and only rarely are giant ulcers encountered measuring between 2 and 4 cm. and involving the entire duodenal bulb. These must, however, be somewhat more common than the reported cases would indicate. Only 9 examples have been reported in the roentgen literature up to the present time and but two of these appear in the American literature. Brdiczka (1), in 1931, reported the first three cases and Knutsson (2), in 1934, added 4 more. Two additional examples were reported by Freedman and Goehring (3), in 1940. As the above authors have emphasized, these huge ulcers are easily overlooked, although one would expect that they would be most easily diagnosed. Their demonstration is of even more importance than the demonstration of a smaller ulcer.

Roentgenographically these giant ulcers closely simulate a normal or slightly abnormal cap and according to E. Freedman the niche may suggest a duodenal diverticulum. The diagnosis in Brdiczka's first 2 cases was missed; in the third patient the experience gained from the 2 earlier cases made possible a correct diagnosis. Of Knutsson's 4 cases, only 2 were correctly diagnosed. In one of his cases histologic examination revealed a carcinomatous ulcer. One of the 2 cases recorded by Freedman and Goehring was diagnosed correctly.

In the case to be reported here the diagnosis was missed only because of lack of experience with this type of lesion. The huge duodenal ulcer crater was clearly shown on the films and was thought to represent a normal cap or a slight questionable deformity. In reality the supposed cap was the ulcer crater (Fig. 1.). The ulcer was the largest yet reported in the radiological literature as far as can be

[1] From the Department of Radiology, Grady Hospital, Atlanta, Ga. Accepted for publication in March 1941.

Fig. 1. Giant ulcer of the duodenum (outlined by arrows). The base of the ulcer appears angular.

determined, measuring 5 × 3 cm. preceding fixation in formalin. Figure 2 shows the specimen after fixation. The linear measurement here has been reduced, by shrinkage, to 4 cm. The diameters as shown in the x-ray film were 4.5 and 3.5 cm.

Brdiczka has called attention to the large persistent niche with an absence of mucosal relief surrounding it in this type of case. The usual radiating mucosal folds are absent because of the size of the crater, which involves an entire wall, and the stretching of the non-ulcerated portion. The crater fills suddenly, the contours are smooth, and the walls are rigid and unchangeable in form. Distal to the niche the pars superior of the duodenum is shortened and narrowed by organic or spastic constriction. In two of Brdiczka's cases this led to the diagnosis of stricture of the duodenum with a normal bulb. Many of the same findings are evident in Figure 1.

CASE REPORT

A white male, aged 36, was admitted in 1932 complaining of abdominal pain, bloody stools, vomiting, and at a later date interscapular pain. He had suffered similar attacks during the preceding year and the history suggested their occurrence over a period of four years.

The patient was seen repeatedly from 1934 to 1940 in various departments of the hospital. The symptoms of ulcer were continuously present but there seemed each time to be some condition that made it difficult to evaluate the signs and symptoms and to make a definite diagnosis. The presence of a rather definite psychogenic factor, the history and laboratory proof of associated syphilis, the in-

Fig. 2. Gross specimen after fixation in formalin. Note the presence of the blood vessel.

constant localization of the pain and tenderness, the misleading negative roentgen findings, and the proof of an abnormally functioning gallbladder—due to the involvement by the ulcer, as later shown by autopsy—were all hindrances to a correct diagnosis.

The attacks of pain and other symptoms were separated, at first, by intervals of six or seven months; for a year the intervals had been only one or two months, and during the week preceding the final admission daily attacks had occurred. A more detailed history follows.

The patient was seen first in March 1932, at which time he complained of headache and pain in the left chest; the physical findings were negative at this time. He stated that he had been in good health until December 1930, at which time he had a "dizzy spell" while at work and was carried home. He was in bed for two weeks with this illness, which he described as "biliousness." He had also been treated for four months for pulmonary tuberculosis but was then told by a physician that he had probably never had the disease.

The patient was next seen in October 1934. He had been seized with a moderately severe cramping pain in the left lower quadrant of the abdomen, which did not radiate or migrate, but was severe enough to make him "fall to the floor." Following this the pain was of a dull aching character. He said that he vomited once and had two bloody stools. He also stated that he had several similar attacks in the past year. He refused to stay in the hospital and was discharged with a diagnosis of acute gastro-enteritis.

He was next seen in April 1939, complaining of pain in the right lower quadrant of the abdomen at two or three day intervals for the preceding three or four months. On the day of admission he had a severe pain between the shoulder blades that lasted only a short time, followed by a continuous rather severe pain in the right lower quadrant. Physical examination revealed tenderness over McBurney's point but nothing else of note. The red blood count was normal; there was a moderate leukocy-

tosis with a slight shift to the left and a marked eosinophilia; the Kahn reaction was 4 plus. The diagnosis was (1) syphilis, (2) possible acute appendicitis, (3) possible intestinal parasites, and (4) malingering.

On July 7, 1940, the patient reported to the Emergency Clinic, complaining of pain in the lower abdomen and back. The physical findings were tenderness in the right upper quadrant and right flank. He was seen repeatedly in the Emergency Clinic during the succeeding week and on one of these visits stated that his pain had shifted to the left upper quadrant. The physical findings now revealed tenderness in the epigastrium and some muscle spasm in this area.

On July 15, 1940, the patient was admitted to the hospital, complaining of severe "stabbing" pains through the abdomen, radiating to the back in the interscapular area, worse upon lying down and about two hours after meals. The pain in the back kept him from sleeping. The admission diagnosis was: (1) possible tabetic crisis, (2) psychoneurosis, (3) cholecystitis, (4) subacute pancreatitis, (5) duodenal ulcer. After ten days' stay in the hospital syphilis of the central nervous system was ruled out. Roentgen examination showed what appeared to be an essentially normal gastro-intestinal tract. The intravenous Graham-Cole test revealed a nonfilling gallbladder. The diagnosis on discharge was (1) chronic cholecystitis, (2) chronic appendicitis, (3) syphilis.

During his stay in the hospital the patient's wife had taken steps to have him admitted to the state hospital for the insane.

Twenty days later he was readmitted to the hospital in a state of shock, having vomited about 3 quarts of blood during the past hour. The medical service believed that they were dealing with a recent duodenal ulcer located posteriorly and now associated with an ominously large arterial leak, probably in the pancreatico-duodenal artery. The surgical consultants believed that laparotomy was contraindicated. The patient was kept alive for seven days by means of transfusions.

At autopsy the pylorus was found to be constricted, measuring 2 cm. in diameter. Just beyond the pylorus was a large excavating ulcer on the posterior surface of the duodenum, oval in shape and measuring 5 × 3 cm. Surrounding this ulcer was a great deal of induration and fibrosis. The crater was necrotic and just off the center of the ulcer the eroded lumen of a blood vessel was seen. This blood vessel communicated directly with the pancreatico-duodenal artery. That portion of the duodenum opposite the ulcer was tightly bound to the gallbladder and the surrounding structures by dense adhesions. The rest of the duodenum was normal except for some hyperemia of the mucosa. The small and large intestines contained large amounts of blood.

The gallbladder wall was thin and pliable except where it was attached to the duodenum. Here there was considerable fibrosis.

Microscopic examination of the ulcer site showed one section consisting mainly of fatty globules interspersed with numerous fibrotic strands. There were numerous blood vessels running through this section and an occasional patch of inflammatory cells. The other section showed only a massive fibrosis throughout and was extremely avascular. In one small area a few chronic inflammatory cells were present.

CONCLUSIONS

Giant ulcers of the duodenum with a diameter of more than 2 cm. are rare, only 9 having been reported in the radiological literature. A tenth example, measuring 5 × 3 cm. in its greatest diameters, is described.

These giant ulcers are easily overlooked on fluoroscopic and radiographic examination for reasons outlined above. In 6 of the 10 cases reported the diagnosis was missed. Judging from this percentage of error, there are probably many other cases not recorded. With the knowledge of their existence and radiographic appearance, more of these giant ulcers should be diagnosed correctly.

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EDITORIAL

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The Case for Inclusive Rates

Inclusive rates or flat rates are rates for hospital services which endeavor to provide complete "hospital" care at a fixed *per diem* charge. Inclusive rates spread the cost of probable expenses over whatever group of patients happens to be hospitalized in a given institution. The patient who does not incur extra expenses helps to pay for the patient who does. When applied to hospital services exclusively, the system may have much to recommend it; at least, numerous articles have been published in hospital journals advocating such procedure. When the system is extended to include medical and surgical services, however, some problems arise which bear analysis.

What medical services should be included? Should they be limited to routine diagnostic medical services or should they include complete medical and surgical services? It is estimated that 90 per cent of a given "hospital" bill represents routine hospital services, and approximately 10 per cent diagnostic medical services, such as radiology and pathology. By a simple extension of the hospital *per diem* charge, general medical and surgical services can be included in a flat rate and, indeed, such rates for tonsillectomy and obstetrical services have actually been used in some institutions. Under such a system the hospital inevitably acts as a middleman in the furnishing of medical services, and for all practical purposes a corporation practises medicine. The hospital competes with the private physician in his office—a paradox, inasmuch as the hospital owes its very existence to the physicians of the community who act on its staff.

The advantages of a flat rate system are convenience in billing, partial predictability of expense, and availability of various medical and surgical services, including laboratory tests, which may or may not truly be indicated.

The disadvantages of an inclusive rate system are as follows:

1. Patients who do not need elaborate diagnostic services and other tests still have to pay their share for such.

2. These special services then tend to be used excessively (experience shows a 100 per cent increase in the use of x-ray and laboratory services). Provision is rarely made for additional technical personnel or supplies and the quality of the diagnostic service therefore suffers. (It is obvious that some patients will have roentgen or clinical laboratory examinations which they might not otherwise receive, but the quality of those examinations is usually so diluted that the ultimate benefit to the majority of patients is *decreased*.)

3. Diagnostic benefits are followed by general surgical benefits: the physicians performing these services are first paid on a fee basis, then on a salary basis. When physicians are on a salary basis (outside of research or special teaching institutions), the hospital usually controls the practice. In times of stress the management tends to cut salaries, rarely to raise them later. The physician finally is picked for the salary he will accept rather than for the qualifications he possesses.

4. After a flat rate has been determined it tends to stay at that level for some years. Though scientific and other developments in the field of medicine may require totally different types of procedure within a few years, the flat rate will tend to preclude

such procedures if they are at all unusual or require elaborate equipment.

5. Flat rate systems do not sell themselves; they must be sold, *i.e.*, advertised; they must be sold in competition with other flat rate services. Claims for this or that institution and its staff begin to develop. Ethics and consideration for the non-hospital-staff physician evaporate.

6. Finally, and most important, the flat rate system is administered by the executive board of the hospital. Many hospital executive boards are composed exclusively of laymen. Some hospital administrators emphasize that "the inclusion of medical men on the board is an undesirable practice." Therefore, if these plans get started in a community, there will be a tendency for a lay board to be in complete control of the medical services in that hospital. When short cuts or economies have to be effected, you may be sure that the hospital costs will not be the first to suffer. The *hospital* is in the practice of medicine.

Flat rates have already been employed in certain institutions for hospital and diagnostic medical services. There is an increasing barrage of propaganda in hospital journals to extend the medical features of the system to complete medical coverage. When this is done, the hospital will dominate the field of medical economics locally. The politician will see a simple way of grasping control not only of hospital care but also of medical care. The interesting thing, therefore, is that *flat rates will actually tend to the socialization of hospitals* as well as of the medical profession. Hospitals, therefore, should themselves be the first to attempt a solution of the problem without recourse to a system which will play directly into the hands of the medical socialists.

What solution is there? One remedy would be to have hospitals print or type clear information sheets in the same manner as do hotels and restaurants. Patients, potential patients, and physicians could then see clearly what the various bed rates are, what the operating room charges may be, the nursing charges, and the average charges for medicines and dressings. The patient can and should be informed that the fees for medical services, whether they be diagnostic x-ray or therapeutic surgical services, vary with the ability of the individual patient to pay and can be discussed by his physician with such other physicians as may be involved, without any loss of efficiency or dignity. The personal interest and attention of a given physician, whether he be radiologist or obstetrician, pathologist or surgeon, are worth far more than any apparent convenience or apparent saving that might be effected by expanding flat rates.

The case for inclusive rates, therefore, does *not exist*. All thinking physicians, and especially hospital administrators and surgeons, should resist this superficially convenient but fundamentally destructive system. If flat rates for "hospital" services are endorsed today, you will see flat rates for complete medical and surgical services tomorrow. Therefore, address yourself to the problem in your own locality. Discuss it with your colleagues and make sure that those physicians who are connected with hospital staffs are apprised of the true facts while there is still time. Eschew a system which would destroy individual initiative and individual enterprise: sickness and sick people cannot be standardized nor put on a department store basis; nor can personal medical attention. If hospitals want flat rates, let them be adopted for purely hospital services (and by that we do not mean pathology or surgery, radiology or obstetrics); keep the latter in the hands of the medical profession, which is trained to use, administer, and develop them.

L. H. G.

AMERICAN BOARD OF RADIOLOGY

The American Board of Radiology is having a new registry of its diplomates printed as of January 1942. If there has been a recent change of address will the diplomates please advise the Secretary, Dr. B. R. Kirklin, Rochester, Minnesota, immediately.

DENVER RADIOLOGICAL CLUB

The newly elected officers of the Denver Radiological Club are: President, Dr. Ernst A. Schmidt; Vice-President, Dr. George A. Unfug; Secretary, Dr. Edward J. Meister; Treasurer, Dr. Leonard G. Crosby. Meetings are held on the third Friday of each month at the Denver Athletic Club.

FLORIDA RADIOLOGICAL SOCIETY

The recently elected officers of the Florida Radiological Society are: President, Dr. J. N. Moore, Ocala; Vice-President, Dr. Elliott M. Hendricks, Fort Lauderdale; Secretary-Treasurer, Dr. Walter A. Weed, Orlando.

The Spring meeting of the Society will be held in connection with the annual meeting of the Florida Medical Association, April 13–15, 1942, at Palm Beach.

VIRGINIA RADIOLOGICAL SOCIETY

At the Annual Meeting of the Virginia Radiological Society the following officers were reelected for the ensuing year: President, Dr. Wright Clarkson, Petersburg; Vice-President, Dr. Clayton Eley, Norfolk; Secretary-Treasurer, Dr. Charles H. Peterson, Roanoke.

Books Received

Books received are acknowledged under this heading, and such notice may be regarded as recognition of the courtesy of the sender. Reviews will be published in the interest of our readers and as space permits.

ALBERS SCHÖNBERGS DIE RÖNTGENTECHNIK [ROENTGEN TECHNIC]. Sixth Edition, completely revised by M. Dorneich, A. Janitzky, L. Drüner, J. Eggert, H. W. Ernst, R. Grashey, L. Grebe, F. Haenisch, R. Janker, B. Rajewsky, Pl. Stumpf. Edited by RUDOLF GRASHEY. Volume I, consisting of 701 pages with 651 illustrations. Published by Georg Thieme, Leipzig, 1941. Price: 44.78 R. M.

CANCER OF THE FACE AND MOUTH: DIAGNOSIS, TREATMENT, SURGICAL REPAIR. By VILRAY P. BLAIR, M.D., SHERWOOD MOORE, M.D., AND LOUIS T. BYARS, M.D., St. Louis. A volume of 599 pages with 260 illustrations and 64 plates. Published by The C. V. Mosby Company, St. Louis, 1941. Price $10.00.

Book Reviews

DIE DEUTUNG DES RÖNTGENSCHICHTBILDES DER LUNGENSPITZEN BEI LUNGENTUBERKULOSE [Interpretation of Tomograms of the Lung Apices in Pulmonary Tuberculosis]. By DR. WILHELM KREMER AND DR. LEONORE RETZLAFF. A volume of 43 pages containing 46 illustrations. Published by Georg Thieme, Leipzig, 1941. Price 3.60 R.M.

In this small atlas the authors attempt to estimate the value of tomography in the demonstration of tuberculous lesions of the apex and also to indicate the pitfalls in the interpretation of "layer roentgenograms." Coronal sections of 1 cm. thickness were made of the formalinized lung at autopsy in cases in which tomography had, during life, indicated an apical lesion. Direct comparison was then possible between the macroscopic appearance of these large sections, the tomogram made at that depth and, in many instances, the ordinary roentgenogram. The superiority of body section roentgenography in demonstrating small cavities and emphysematous blebs is well established. In addition, there is a good description of the difficulties of interpretation of tomograms and the shadows which normal structures produce in this type of roentgenogram.

DIE WIRBELSÄULENVERLETZUNGEN UND IHRE AUSHEILUNG [Vertebral Injuries and Their Healing]. By DR. ALFONS LOB, Navy Staff Physician of the German Reich, with an introduction by DR. G. MAGNUS of Munich. A monograph of 182 pages with 289 illustrations. Published by Georg Thieme, Leipzig, 1941. Price 28.50 R.M.

This book is another of a series of monographs devoted to the subject of vertebral fractures and their healing. The author has covered the subject with the minute detail characteristic of these monographs. The changes taking place after fractures of vertebral bodies are well described, in interesting detail, and fully illustrated. An up-to-date note on the long-discussed syndrome known as "Kümmell's

disease" is contained in the work. A chapter on the changes noted experimentally in animals with traumatic lesions of vertebrae is another interesting portion.

As is usual in these monographs, the detail of description is elaborate. The illustrations are excellently reproduced, and abundant roentgenograms both from life and of pathologic specimens illustrate well the points described by the author. Numerous photographs of specimens are included and many photomicrographs, showing well the histologic detail.

All in all, this is a well worth-while monograph for use by those interested in injuries to vertebrae.

DIE DIFFERENTIALDIAGNOSE DER WIRBELSÄULENTUBERKULOSE [The Differential Diagnosis of Vertebral Tuberculosis]. By PRIV. DOZ. DR. J. E. W. BROCHER. A monograph of 88 pages with 129 illustrations. Published by Georg Thieme, Leipzig, 1941. Price 14.60 R.M.

This is another of the series of monographs and atlases published by the house of Thieme covering various subjects of interest to radiologists. It is, like all the others seen by the reviewer, well printed, with fine illustrations, on excellent paper.

The text is brief. It contains a short summary of the facts known concerning tuberculous spondylitis as well as the various lesions of the vertebrae with which this condition may be confused. Such conditions as non-tuberculous spondylitis, adolescent kyphosis, the scalenus anticus syndrome, various congenital anomalies of vertebrae, osteoporosis, and tumors, are described briefly and concisely and all are well illustrated.

This is a useful atlas for those who are particularly interested in diseases of the spinal column.

BULLETIN OF THE AMERICAN COLLEGE OF RADIOLOGY

Points of Interest

The following bulletin was sent to State Councilors of the American College of Radiology and secretaries of all regional radiological societies on August 27:

A. M. A. RESOLUTION

At its June meeting in Cleveland, the House of Delegates of the American Medical Association instructed the Board of Trustees to confer with representatives of the American Hospital Association and the Protestant and Catholic hospital associations to clarify the relation of medical services in prepayment hospitalization and similar plans, "the same to be in line with the basic principles laid down in the past by the House of Delegates." These basic principles expressly demand that radiology be treated as a medical service and not included as a part of hospital service along with benefits offered in group hospitalization.

The House of Delegates also approved the report of a reference committee recommending that "special societies, such as radiologists, pathologists, and anesthesiologists, recommend to their members that they defer entering into contractual relationships with hospitals involved in medical service plans until the relationship has been thoroughly clarified. . . . ."

Also approved was a resolution recommending that "wherever obtainable, hospitals should have doctors of medicine especially trained in pathology, radiology, anesthesiology, and physical medicine as directors in charge of these respective departments, and that the directors of these departments shall be eligible for membership on their respective medical staffs or medical boards with voice and vote."

HOSPITAL EXPLOITATION

Of especial interest to radiologists is an article under the title "The Patient Comes First," appearing in the August *Atlantic Monthly*, by Dr. Miles Atkinson, a New York surgeon who came to this country from England a few years ago. In discussing the parlous state of over-capitalized hospitals, Doctor Atkinson concludes that they have resorted to some dubious practices. He says: "Another widespread practice that is generally accepted, though it is difficult to see why, is that of working the pathological and x-ray departments deliberately at a profit—the charges are such that income is higher than expenses. The difference, or the profit, goes into the funds of the institution. As it was put very truly in a medical paper not long ago, 'The arithmetical difference between the total cost of operation and the total profit derived . . . . is certainly represented by the individual services of the medical personnel'; but funds which represent professional training and specialist knowledge are diverted from the doctors to the institution."

MEDICAL SERVICE PLANS

More state medical societies are following the precedent of California, Michigan, New Jersey, and New York and are preparing to install prepayment medical service plans for groups of employed subscribers in designated low income brackets. In connection with these plans, two points are of paramount interest to radiologists: (1) Radiology should be included along with other medical services whether the plan embraces complete medical care or is for hospitalized surgery alone; it should not be included as a part of hospital care in the benefits paid for hospitalization. (2) Some deterrent should be placed upon the use of roentgen diagnosis, else the expenses for this service alone may render the plan actuarially unsound. A maximum allowance for radiology may be determined, or the subscribers may be required to pay a certain portion of fees charged for roentgen diagnosis.

Anent the subject of medical service plans, an interesting article, "But Health Insurance is Different," by Nathan Sinai, appears in the August *Harpers*, page 275.

NYA

The NYA program calling for chest examinations on some 500,000 youths in the country each year is undergoing sporadic development in various sections of the country. It appears that plans and procedures are subject to the discretion of the NYA director in each state. In some states the program is well under way, while in others nothing has been done. In Iowa, Virginia, Florida, and a few other states, an agreed method and rate for reimbursement of radiologists performing chest examinations have been adopted. In several states radiologists have decided against working at the hourly rates allowed by NYA and have preferred to let the chest examinations be performed by public agencies or tuberculosis associations. This subject was discussed at great length by the Board of Chancellors of the College during its meeting in June, and it was decided that the decision on this matter should be left to the radiological societies in each locality.

LOCUM TENENS CONTRACTS

In our bulletin of April 16, 1941 (RS-61) we submitted the resolution adopted by the College pertaining to the protection of civil practices of radi-

ologists called for military duty.[1] In that bulletin we recommended that a radiologist leaving a hospital practice make a personal contract with his locum tenens instead of permitting the hospital to select someone to fill his position during his absence. Such contracts should be prepared only with the assistance of a competent attorney, and should include provisions for disposition of income from the practice and a restrictive covenant to protect the absentee's practice after he returns to the community. For a general discussion of locum tenens contracts, see *Medical Economics* for July 1941, page 42. Members wishing sample or suggested contracts for a locum tenens should write to the headquarters office of the College.

MILITARY AFFAIRS

No very definite estimate of the number of radiologists that will be required for the armed forces, either for defense or war, has been forthcoming from military circles. Neither have we any accurate idea of the number of radiologists already called to active duty. The contact of the College with responsible Army and Navy officials has been less than satisfactory, and this subject was a matter of lengthy discussion during the last meeting of the Board of Chancellors. Vincent W. Archer, Chairman of the Board, has asked the present Advisory Committee on Radiology to the National Research Council to act as the College Committee on Military Affairs. Henceforth it will be the point of contact between organized radiology and national defense agencies. The committee is composed of Dr. A. C. Christie, chairman, Dr. B. R. Kirklin, Dr. U. V. Portmann, and Dr. W. Edward Chamberlain.

INTER-SOCIETY COMMITTEE

Pursuant to amendments to the Constitution and By-Laws of the College, the activities carried on by the Inter-Society Committee for Radiology for the past three years have been taken over by the College. At its last meeting the Board of Chancellors enlarged the Inter-Society Committee by adding to it the representatives on the Board of Chancellors nominated by the American Roentgen Ray Society, the Radiological Society of North America, and the American Radium Society. Now called the Inter-Society Commission on Economics, the committee is composed of the original three, Dr. A. C. Christie, Dr. E. H. Skinner, and Dr. L. S. Goin, with the addition of Dr. E. L. Jenkinson, Chicago, Dr. L. H. Garland, San Francisco, and Dr. F. W. O'Brien, Boston.

GROUP HOSPITALIZATION

For years organized radiology has warned that the specter of hospital domination and exploitation is a threat to the integrity of all medicine. Full appreciation of this fact has not always been manifested when radiologists appealed for support from their local colleagues in a fight to keep radiology from being offered as a part of hospital care among benefits in a group hospitalization plan. Of late an increasing number of leaders in organized medicine have come to the realization that we were not merely crying "Wolf!" An editorial in *Medical Economics* for August (page 20) is of interest: "When the first of the three resolutions referred to was introduced at the St. Louis convention (of the A. M. A.) in 1939, it related almost exclusively to the status of radiologists, pathologists, and anesthesiologists; for these were about the only medical men whose services were likely to be included in a group hospitalization policy. Since then, conditions have changed materially. Hospital groups are now putting the finishing touches on a vast new prepayment plan which, it is predicted, will provide millions of low-income citizens with both hospitalization and medical care. This is bound to affect not only the physicians in the three specialties named but—more important—all physicians in virtually all other branches of medicine."

MAC F. CAHAL
Executive Secretary

[1] See RADIOLOGY **37:** 110, July 1941.

RADIOLOGICAL SOCIETIES OF NORTH AMERICA

Editor's Note.—Will secretaries of societies please co-operate with the Editor by supplying information to keep these notices accurate and up to date? Please send information to Howard P. Doub, M.D., Henry Ford Hospital, Detroit, Mich.

UNITED STATES

Radiological Society of North America.—Secretary, D. S. Childs, M.D., 607 Medical Arts Building, Syracuse, N. Y. Annual Meeting, Dec. 1–5, 1941, San Francisco, Calif.

American Roentgen Ray Society.—Secretary, C. B. Peirce, Royal Victoria Hospital, Montreal, Canada.

American College of Radiology.—Secretary, Mac F. Cahal, 540 N. Michigan Ave., Chicago, Ill. Annual Meeting, 1942, Atlantic City, N. J.

Section on Radiology, American Medical Association.—Secretary, Dr. J. T. Murphy, 421 Michigan St., Toledo, Ohio. Annual Meeting, 1942, Atlantic City, N. J.

CALIFORNIA

California Medical Association, Section on Radiology.—Secretary, Joseph D. Coate, M.D., 434 Thirtieth St., Oakland.

Los Angeles County Medical Association, Radiological Section.—Secretary, Wilbur Bailey, M.D., 2007 Wilshire Blvd.; Meets second Wednesday of each month at County Society Building.

Pacific Roentgen Society.—Secretary-Treasurer, L. Henry Garland, M.D., 450 Sutter St., San Francisco. Society meets annually during annual meeting of the California Medical Association.

San Francisco Radiological Society.—Secretary, J. Maurice Robinson, M.D., University of California Hospital. Meets monthly on third Thursday at 7:45 P.M., for the first six months at Toland Hall (University of California Medical School) and for the second six months at Lane Hall (Stanford University School of Medicine).

COLORADO

Denver Radiological Club.—Secretary, Edward J. Meister, 366 Metropolitan Bldg. Meetings third Friday of each month at the Denver Athletic Club.

CONNECTICUT

Connecticut State Medical Society, Section on Radiology.—Secretary-Treasurer, Max Climan, M.D., 242 Trumbull St., Hartford. Meetings bimonthly, on second Thursday. Place of meeting selected by Secretary.

FLORIDA

Florida Radiological Society.—Secretary-Treasurer, Walter A. Weed, M.D., 204 Exchange Building, Orlando. The next meeting will be at the time of the annual meeting of the Medical Association of Florida, April 13-15, 1942, at Palm Beach.

GEORGIA

Georgia Radiological Society.—Secretary-Treasurer, Robert C. Pendergrass, M.D., Prather Clinic Bldg., Americus. Meetings twice annually, in November and at the annual meeting of the Medical Association of Georgia in the spring.

ILLINOIS

Chicago Roentgen Society.—Secretary, Chester J. Challenger, M.D., 3117 Logan Blvd. The Society meets at the Palmer House on the second Thursday of October, November, January, February, March, and April.

Illinois Radiological Society.—Secretary-Treasurer, William DeHollander, M.D., St. Johns' Hospital, Springfield. Meetings quarterly by announcement.

Illinois State Medical Society, Section on Radiology.—Secretary, Earl E. Barth, M.D., 303 E. Chicago Ave., Chicago.

INDIANA

The Indiana Roentgen Society.—Secretary-Treasurer, Harold C. Ochsner, Methodist Hospital, Indianapolis. Annual meeting in May.

IOWA

The Iowa X-ray Club.—Holds luncheon and business meeting during annual session of Iowa State Medical Society.

KENTUCKY

Kentucky Radiological Society.—Secretary-Treasurer, Joseph C. Bell, M.D., 402 Heyburn Bldg., Louisville. Meeting annually in Louisville, third Sunday afternoon in April.

LOUISIANA

Louisiana Radiological Society.—Secretary-Treasurer, Johnson R. Anderson, M.D., North Louisiana Sanitarium, Shreveport. Meets annually at same time as State Medical Society. Next meeting, New Orleans, April 1942.

Shreveport Radiological Club.—Secretary-Treasurer, W. R. Harwell, M.D. Meetings monthly on the second Wednesday, at the offices of the various members.

MARYLAND

Baltimore City Medical Society, Radiological Section.—Secretary, Walter L. Kilby, M.D., 101 W. Read St. Meetings are held the third Tuesday of each month.

MICHIGAN

Detroit X-ray and Radium Society.—Secretary-Treasurer, E. R. Witwer, M.D., Harper Hospital, Detroit. Meetings first Thursday of each month from October to May, inclusive, at Wayne County Medical Society club rooms, 4421 Woodward Ave., Detroit.

Michigan Association of Roentgenologists.—Secretary-Treasurer, J. E. Lofstrom, M.D., St. Mary's Hospital, Detroit. Meetings quarterly by announcement.

MINNESOTA

Minnesota Radiological Society.—Secretary, John P. Medelman, M.D., 572 Lowry Medical Arts Bldg., St. Paul. Meetings quarterly.

MISSOURI

The Kansas City Radiological Society.—Secretary, P. E. Hiebert, M.D., 907 North Seventh St. (Huron Bldg.), Kansas City, Kansas. Meetings last Thursday of each month.

The St. Louis Society of Radiologists.—Secretary, Wilbur K. Mueller, M.D., University Club Bldg. Meets on fourth Wednesday of October, January, March, and May, at a place designated by the president.

NEBRASKA

Nebraska Radiological Society.—Secretary, D. A. Dowell, M.D., 816 Medical Arts Bldg., Omaha. Meetings third Wednesday of each month at 6 P.M. in either Omaha or Lincoln.

NEW ENGLAND

New England Roentgen Ray Society (Maine, New Hampshire, Vermont, Massachusetts, and Rhode Island).—*Secretary,* Hugh F. Hare, M.D., Lahey Clinic, Boston, Mass. Meets monthly on third Friday at Boston Medical Library.

NEW JERSEY

Radiological Society of New Jersey.—Secretary, H. J. Perlberg, M.D., Trust Co. of New Jersey Bldg., Jersey City. Meetings at Atlantic City at time of State Medical Society and midwinter in Newark as called by president.

NEW YORK

Associated Radiologists of New York, Inc.—Secretary, William J. Francis, M.D., 210 Fifth Ave., New York City. Regular meetings the first Monday evening of the month in March, May, October, and December.

Brooklyn Roentgen Ray Society.—Secretary-Treasurer, Leo Harrington, M.D., 880 Ocean Ave. Meetings held the fourth Tuesday of every month, October to April.

Buffalo Radiological Society.—Secretary-Treasurer, Joseph S. Gianfranceschi, M.D., 610 Niagara St. Meetings second Monday evening each month, October to May, inclusive.

Central New York Roentgen Ray Society.—Secretary-Treasurer, Carlton F. Potter, M.D., 425 Waverly Ave., Syracuse. Meetings are held in January, May, and October, as called by Executive Committee.

Long Island Radiological Society.—Secretary, Marcus Wiener, M.D., 1430 48th St., Brooklyn. Meetings fourth Thursday evening each month at Kings County Medical Bldg.

New York Roentgen Society.—Secretary, Paul C. Swenson, M.D., Presbyterian Hospital, New York, N. Y.

Rochester Roentgen-ray Society.—Secretary, S. C. Davidson, M.D., 277 Alexander St. Meetings at convenience of committee.

NORTH CAROLINA

Radiological Society of North Carolina.—Secretary-Treasurer, Major I. Fleming, M.D., 404 Falls Road, Rocky Mount. Meeting with State meeting in May, and meeting in October.

NORTH DAKOTA

North Dakota Radiological Society.—Secretary, L. A. Nash, M.D., St. John's Hospital, Fargo. Meetings by announcement.

OHIO

Ohio Radiological Society.—Secretary, J. E. McCarthy, M.D., Cincinnati. The next meeting will be held at the time and place of the annual meeting of the Ohio State Medical Association.

Cleveland Radiological Society.—Secretary-Treasurer, J. O. Newton, M.D., 13921 Terrace Road, East Cleveland. Meetings at 6:30 P.M. at the Mid-day Club, in the Union Commerce Bldg., on fourth Monday of each month from October to April, inclusive.

Radiological Society of the Academy of Medicine (Cincinnati Roentgenologists).*—Secretary-Treasurer,* Justin E. McCarthy, M.D., 707 Race St. Meetings held third Tuesday of each month.

PENNSYLVANIA

Pennsylvania Radiological Society.—Secretary-Treasurer, L. E. Wurster, M.D., 416 Pine St., Williamsport. The Society meets annually; time and place of next meeting will be announced later.

The Philadelphia Roentgen Ray Society.—Secretary, Barton R. Young, M.D., Temple University Hospital, Philadelphia. Meetings held first Thursday of each month at 8:15 P.M., from October to May, in Thomson Hall, College of Physicians, 21 S. 22nd St., Philadelphia.

The Pittsburgh Roentgen Society.—Secretary-Treasurer, Harold W. Jacox, M.D., 4800 Friendship Ave., Pittsburgh, Pa. Meetings are held on the second Wednesday of each month at 4:30 P.M., from October to June, at the Pittsburgh Academy of Medicine, 322 N. Craig St.

ROCKY MOUNTAIN STATES

Rocky Mountain Radiological Society (North Dakota, South Dakota, Nebraska, Kansas, Texas, Wyoming, Montana, Colorado, Idaho, Utah, New Mexico).*—Secretary,* A. M. Popma, M.D., 220 North First St., Boise, Idaho.

SOUTH CAROLINA

South Carolina X-ray Society.—Secretary-Treasurer, Malcolm Mosteller, M.D., Columbia Hospital, Columbia. Meetings in Charleston on first Thursday in November, also at time and place of South Carolina State Medical Association.

TENNESSEE

Memphis Roentgen Club.—Chairmanship rotates monthly in alphabetical order. Meetings second Tuesday of each month at University Center.

Tennessee Radiological Society.—Secretary-Treasurer, Franklin B. Bogart, M.D., 311 Medical Arts Bldg., Chattanooga. Meeting annually with State Medical Society in April.

TEXAS

Texas Radiological Society.—Secretary-Treasurer, L. W. Baird, M.D., Scott and White Hospital, Temple. Meets annually.

VIRGINIA

Virginia Radiological Society.—Secretary, Charles H. Peterson, M.D., 603 Medical Arts Bldg., Roanoke.

WASHINGTON

Washington State Radiological Society.—Secretary-Treasurer, Kenneth J. Holtz, M.D., American Bank Bldg., Seattle. Meetings fourth Monday of each month at College Club, Seattle.

WISCONSIN

Milwaukee, Roentgen Ray Society.—Secretary-Treasurer, Irving I. Cowan, M.D., Mount Sinai Hospital, Milwaukee. Meets monthly on first Friday at the University Club.

Radiological Section of the Wisconsin State Medical Society.—Secretary, Russel F. Wilson, M.D., Beloit Municipal Hospital, Beloit. Two-day annual meeting in May and one day in connection with annual meeting of State Medical Society, in September.

University of Wisconsin Radiological Conference.—Secretary, E. A. Pohle, M.D., 1300 University Ave., Madison, Wis. Meets every Thursday from 4 to 5 P.M., Room 301, Service Memorial Institute.

CANADA

Section on Radiology, Canadian Medical Association.—Secretary, W. J. Cryderman, M.D., Medical Arts Bldg., Toronto.

Section on Radiology, Ontario Medical Association.—Secretary, W. J. Cryderman, M.D., 474 Glenlake Avenue, Toronto.

Canadian Association of Radiologists.—Honorary Secretary-Treasurer, A. C. Singleton, M.D., Toronto.

La Société Canadienne-Française d'Eléctrologie et de Radiologie Médicales.—General Secretary, Origène Dufresne, M.D., Institut du Radium, Montreal. Meetings are held the third Saturday of each month, generally at the Radium Institute, 4120 East Ontario Street, Montreal; sometimes, at homes of members.

CUBA

Sociedad de Radiología y Fisioterapia de Cuba.—Offices in Hospital Mercedes, Havana. Meetings are held monthly.

ABSTRACTS OF CURRENT LITERATURE

ROENTGEN DIAGNOSIS

The Chest

The Digestive Tract

The Skeletal System

The Genito-Urinary Tract

The Central Nervous System

Foreign Bodies

Air Raid Casualties

Technic

RADIOTHERAPY

Malignant Neoplasms

Non-Malignant Conditions

Technic and Dosage

ROENTGEN DIAGNOSIS

THE CHEST

Acute Pneumonitis: Report of 87 Cases among Adolescents. J. Roswell Gallagher. Yale J. Biol. & Med. **13:** 663–677, May 1941.

The author reviews his experiences with 87 cases of acute pulmonary infection observed among groups of adolescents during the past seven years. He believes that the designation acute pneumonitis should be used to distinguish this condition from ordinary bronchopneumonia, from the primary bronchopneumonias of childhood, and from secondary bronchopneumonias which follow measles, whooping cough, etc. While the disease is infectious, in his experience it has reached epidemic proportions during only one year. The incubation period is relatively long; his findings suggest it to be from seven to twenty days. Presenting symptoms are usually malaise, headache, and a slight cough; there are no physical signs except fever, and leukocytosis is slight or absent. As the disease develops, x-ray findings become positive. The physical signs in the chest rarely ever reach the proportions to be expected from the x-ray findings. Prostration is minimal, the illness rarely extending more than one week.

In practically all the author's cases chest films were obtained on the day of admission. The majority of the lesions appear to originate at the hilum and then spread outward along the main bronchus fanwise, either laterally toward a base or toward an apex. Several lesions appeared to originate in either base. The area of consolidation was usually of considerable extent and of greater degree than the clinical picture would indicate.

Bacteriological examination of the sputum has been quite unsatisfactory and has shown only the bacteria commonly found in the mouth flora. The author's work, together with the work of other investigators, indicates that the etiological factor may be a virus or of rickettsial origin.

Treatment in the series reported was symptomatic. The food intake was determined by the patient's appetite. The fluid intake was kept between 3,000 and 4,000 c.c. daily. In only three cases, of a relatively severe form, was sulfanilamide given. It was found to be without any evident benefit.

ANDREW H. DOWDY, M.D.

Recurrent Spontaneous Pneumothorax. Henry G. Hadley. Dis. of Chest. **7:** 166–172, May 1941.

When infectious processes such as tuberculosis or tumors of the lung, which destroy lung tissue, are not sufficiently advanced for the development of a clinical picture of the primary disease, as well as in asthma, chronic emphysema, and cystic disease of the lungs, spontaneous—or so-called spontaneous—pneumothorax may occur. Other less obvious conditions disturb the continuity of the visceral pleura and result in pneumothorax. The author discusses the treatment of such cases and presents brief histories of five patients seen first in his office. Nothing is added to our knowledge of the complications and clinical course of this condition.

WM. H. GILLENTINE, M.D.

High Spots in Bronchiectasis. P. B. Goodwin. Illinois M. J. **79:** 426–430, May 1941.

The author gives a brief review of the etiology, symptoms, pathology, and treatment of bronchiectasis. He calls attention especially to the necessity for the radiologist to familiarize himself thoroughly with the history and clinical, laboratory, and physical findings if he is to be of the greatest aid as a consultant in interpretation of the x-ray film. The frequent co-existence of paranasal sinus disease and bronchiectasis is emphasized. Attention is also called to the need of more roentgen therapy in chronic inflammatory diseases such as bronchiectasis. Longer courses of treatment are recommended, as for example three months, through anterior, posterior, and lateral fields, with an average dosage of 1,200 r to each field.

WILLIS A. WARD, M.D.

Intrathoracic Malignancy in Children. Samuel Goldberg and Jacob Wallen. Arch. Pediat. **58:** 228–242, April 1941.

Goldberg and Wallen point out that the diagnosis of intrathoracic carcinoma in children may be attended by considerable difficulty. They do not care for the embryologic nomenclature, the tumors being undoubtedly influenced by acquired characteristics of the cells rather than by their embryologic derivation, and the neoplastic cells often losing their original cell potencies and taking on characteristics of parasitic cells and tissues depending on their location and nutrition.

The histologic classification is therefore employed; Reisser, having thoroughly reviewed the literature, cited 45 authentic cases in children, with the following classification:

6 carcinomas (5 lung, 1 pleura)	13%
18 sarcomas (16 lung, 2 pleura)	40%
11 lymphosarcomas (mediastinum, lung, and pleura)	25%
4 cysts of lungs (benign)	9%
3 ganglioneuromas (of thoracic segment of sympathetic nerves)	6%
1 teratoma of mediastinum	2%
1 lipoma of mediastinum	2%
1 papilloma of mediastinum	2%

The ages in this series varied from seven weeks to fifteen years and the cases were equally distributed in the age groups. Some observers have found a greater incidence during the first six years. Males predominate slightly. The left side is affected somewhat more often than the right, though not all observers are in accord on this point.

Metastasis was almost universal, either to neighboring structures or to external nodes, liver, spleen, bone marrow, etc. The average duration was from one to one and a half years. In very young infants having teratomas or cysts of the lung, pulmonary embarrassment was marked and led rapidly to death.

The lymphosarcomas respond temporarily to roentgen therapy, after which the symptoms recur.

Ganglioneuromas in the chest have been reported only in recent years. According to Langdon, tumors arising from neural tissue may be benign or malignant depending on whether they arise from the mature or immature cells constituting the sympathetic or parasympathetic systems. The immature tumors are more common in childhood, the mature-cell tumors in more advanced ages. Ganglioneuromas are usually solitary, circumscribed, subpleural, with the base on the vertebral column, the pleura forming a sac about them. The size may vary from that of an egg to a grapefruit. Usually they are not infiltrative. They may, however, invade the vertebral canal. Paralysis of the lower extremities by pressure has been reported, Horner's syndrome has been noted.

Two case reports are included. The first patient, aged nine, had cervical adenopathy and a large pleural effusion on the left demonstrated by x-rays. The

tentative diagnosis was "left-sided empyema." Aspiration of the left pleural cavity yielded bloody fluid, after which x-rays showed a homogeneous shadow in the left chest strongly suggestive of a malignant growth. Regression followed x-ray therapy, but exacerbation ensued, and operation was performed. At autopsy the growth was found to be a lymphosarcoma.

The second patient, aged twelve, was admitted with a diagnosis of pleural effusion. Aspiration yielded bloody fluid containing tumor cells. Operation revealed a lymphosarcoma of the mediastinum. The child survived for two months following operation.

Among the conclusions enumerated by the authors are the following: X-ray is the most dependable source of information. Metastasis is most marked in lymphosarcomas. Pleural effusion is seen in about one-third of the cases. PERCY J. DELANO, M.D.

Differentiation of Bronchiogenic Carcinomas. Paul W. Gebauer. J. Thoracic Surgery **10:** 373, April 1941.

This paper is based on 216 cases diagnosed as primary bronchiogenic carcinoma at the Cleveland City Hospital; 158 were proved histologically. The tumors were of three types, small-cell carcinomas, 53; adenocarcinomas, 32; squamous-cell carcinomas, 61. Five were called carcinoma simplex and in 7 there was insufficient material for histologic diagnosis of the tumor type. Late in the disease the author believes it is possible to differentiate these three main types of tumor before histological verification in 60 per cent of the whole group and in 90 per cent of the squamous carcinomas. The main points of differentiation are as follows:

Small-cell Carcinoma: Of this group, 66 per cent arise in the main stem bronchi; only rarely do these tumors originate in a small branch bronchus. The formation of a mediastinal mass is characteristic of this centrally located and rapidly growing tumor. Metastasis occurs early, to the mediastinal nodes and occasionally to more distant nodes or the brain. The average age is forty-seven, patients of this group being the youngest of the three types. Cough and chest pain come early, with hemoptysis, hoarseness, dysphagia, and compression of the vena cava appearing later. Roentgenologically the mass appears to blend with the mediastinum. Atelectasis is not common. Bronchoscopically there are distortion and fixation. The carina is widened and rounded. The mediastinal mass may compress and occlude the bronchial lumen or the involved bronchus may be filled with tumor tissue, providing ample opportunity for biopsy. Because of the gross nature of this lesion, there is little hope that many cases will be cured by excision.

Adenocarcinoma: Seventy per cent of the adenocarcinomas arise in the secondary branches and only 10 per cent in the main stem bronchi. These tumors tend to extend peripherally rather than centrally. A well circumscribed mass is often present. There may be widespread and extensive blood-borne metastases, as well as lymphatic metastases. Hemoptysis and pleural pain are early symptoms. Often the presenting complaint is due to distant metastases. The average age of these patients is fifty-one years; 28 per cent of the series were females, in contrast to 5 per cent for each of the other two types. Radiographically a well circumscribed mass may be seen separate from the mediastinum. Occasionally the primary nodule may be hidden by mediastinal structures and oftentimes late in the disease the lungs are full of secondary nodules. Bronchoscopy may be entirely negative. These peripheral tumors are most favorable for excision but inaccessible for biopsy.

Squamous-cell Carcinoma: Of these tumors 70 per cent arise in the first branches of the main stem bronchi. The average age is fifty-five years. The tumor grows slowly and metastasizes late. Central necrosis in the tumor with cavitation is common, occurring in over 50 per cent of the cases. Tumors high in the apex invade the chest wall, producing the so-called "Pancoast tumor." A simple lobar or lobular atelectasis is evident on the roentgenogram besides the tumor itself, which is not peripheral and not sharply circumscribed. These cases are best suited for surgical removal. When the tumor is in the lower lobes bronchoscopic biopsy can be done and wide resection is feasible.

In this series a positive biopsy specimen was obtained in 72 per cent of more than 100 bronchoscopies and similar figures are found in the literature. These figures are misleading, however, as they do not take into account the stage of the disease when the bronchoscopy is done and they cannot be applied to patients examined at the onset of symptoms. In all probability, if performed early, bronchoscopy will be negative in about 40 to 50 per cent of cases. A negative bronchoscopy means only that bronchography, sputum examination for tumor cells, aspiration biopsy, thoracoscopy, and finally surgical exploration may be necessary. The author believes that, in general, symptoms occur early in the disease and all available methods of examination should be employed if necessary, at this time. HAROLD O. PETERSON, M.D.

War Wounds of the Chest. Douglas Robb. New Zealand M. J. **40:** 109–112, April 1941.

The importance of chest wounds among war injuries is demonstrated by the fact that, according to Kenneth Walker (Proc. Roy. Soc. Med. **33:** 607, 1940) 60 per cent of all war casualties are chest injuries. In the World War Sauerbruch found that of 300 dead on the battle field 37 per cent had chest injuries. Basing his recommendations both on this high mortality and on the marked reduction of fatal cranial injuries after the introduction of the steel helmet, Walker advocates the use of a light body armor for soldiers, a recommendation which apparently so far has been neglected by all army commands.

Three prominent types of chest injury are described. The first type—blast injuries due to proximity to a violent explosion—results in serious lung damage without any injury to either the soft or bony parts of the chest wall. Severe compression of the lung by the in-driven chest wall is considered the principal cause, and small hemorrhages, often confluent, are observed in the lung parenchyma. Clinical symptoms, among them hemoptysis and hemothorax, may be delayed for one or more days. The best prophylaxis consists in the prone position behind a substantial structure. Therapeutic pneumothorax has proved valuable in the treatment of some of these cases.

The second type includes the severe injuries to the heart, great vessels, the diaphragm, or the adjoining organs of the upper abdomen. These injuries generally result from fragments of high explosives or from falling masonry and are, as a rule, rapidly fatal.

The third type is represented by small penetrating bullet wounds. The prognosis and treatment of these cases vary according to location of injury and complications. The most common complications are sterile or infected hemothorax, open "sucking" pneumothorax, presence of an intrathoracic foreign body, and damage to diaphragm, liver, spleen, etc.

The therapeutic procedure depends largely on the transport and hospital facilities. While the experiences of the Spanish civil war favored abolition of first-aid stations and the immediate transport of casualties to the nearest hospital, this system, in order to be effective, requires the proximity of towns with well equipped hospitals.

The author stresses the value of adequate x-ray facilities in the diagnostic and therapeutic classifica-

tion and evaluation of chest injuries and concludes that the maxim of Pierre Duval (1917) still holds good regarding operative intervention: "Leave bullet wounds alone; always operate on shell wounds."

ERNST A. SCHMIDT, M.D.

Development of the Fetal Lung, with Special Reference to the Lining of the Alveoli and the Effect of Immaturity on Respiration. Robert F. Norris, Thomas T. Kochenderfer, and Ralph M. Tyson. Am. J. Dis. Child. **61:** 933–950, May 1941.

An anatomic study of the fetal lung was made to determine what bearing immaturity might have on respiratory failure in infants born prematurely. Twenty-two infants varying from four lunar months gestation to full term were studied. Body length ranged from 15 to 53 cm. Reconstructions from the injected lungs of fetuses with a body length of 15, 25, and 48 cm., respectively, indicated that subdivision of the respiratory elements is not symmetric or invariably dichotomous and that not all subdivisions of the lung go through the same number of developmental stages.

The development of the lung as a whole, however showed a degree of maturity which corresponded closely with that of the body as a whole. It was found that before the gestation age of five to six lunar months the terminal air sacs have an obvious epithelial lining and that the mesenchymal capillaries have not penetrated to the potential air spaces. After this age, protrusion of the mesenchymal capillaries between the epithelial cells of the primitive air sacs gradually takes place, and the epithelium of the terminal air sacs is gradually lost, until at term the normal alveoli contain no visible epithelium. It is the opinion of the authors that after birth the alveoli normally have no epithelial lining.

The conclusion of the authors is that before the gestation age of five to six lunar months the obvious epithelial lining of the terminal air sacs and the position of the mesenchymal capillaries at a distance from the potential air spaces are great impediments to respiration.

GEORGE M. WYATT, M.D.

THE DIGESTIVE TRACT

Some Radiological Observations on Post-Cricoid Obstruction and Anaemia. A. S. Johnstone. Brit. J. Radiol. **14:** 177–180, May 1941.

The combination of microcytic anemia and dysphagia—the so-called Plummer-Vinson syndrome—is usually found in women at the menopausal age or later. Repeated blood loss, sometimes aggravated by a gynecological condition, may produce a severe anemia. These patients usually have, also, an achlorhydria. They develop an atrophic gastritis, which often involves the esophagus. The atrophy of the esophageal mucosa gives rise to the formation of webs and constricting bands producing dysphagia. The dysphagia reduces the intake of food, which further aggravates the condition. Malignant change is sometimes seen.

The webs can usually be seen on fluoroscopy but are very difficult to reproduce on films because they occur high in the esophagus. The entire gastro-intestinal tract should be examined to discover any other organic disease. Four cases are very briefly reported.

SYDNEY J. HAWLEY, M.D.

Regional Ileitis. G. Friedlaender. Brit. J. Radiol. **14:** 164–169, May 1941.

Although cases of regional ileitis were reported in the literature sporadically in the early nineteenth century, it was not recognized as a disease entity until the work of Crohn, Ginzburg and Oppenheimer in 1932 (J. A. M. A. **99:** 1323, 1932). The original report was of disease in the terminal ileum. Since then it has been found elsewhere in the small intestine and in the large. Slightly more than half the cases occur in males. The majority of patients are between the ages of eleven and forty.

In the early stages the wall of the bowel is thickened, reddened, and edematous. There are superficial ulcerations on the mucosa, especially along the mesenteric attachment. The mucosa and submucosa are infiltrated with inflammatory tissue. In the advanced stages the wall of the bowel becomes rigid, the lumen usually being narrowed. The wall is infiltrated with fibroblasts, round cells, and plasma cells, and there is hypertrophy of the muscularis. Grossly the appearance resembles hyperplastic tuberculosis, but tubercle bacilli cannot be demonstrated. Ulceration is common. Abscesses and fistulae are frequent.

Clinically in the early stages the symptoms are those of an acute inflammatory process in the abdomen, frequently simulating appendicitis. In the later stages there are abdominal pain, diarrhea, tenderness, fever, and sometimes intestinal obstruction.

The diagnosis is best made by x-ray examination with a barium meal. The small intestine should be examined at frequent intervals during the passage of the barium. Alterations in the mucosal pattern, narrowing and irregularity of the lumen of the bowel, and absence of peristalsis are the typical findings.

The treatment is surgical, the present tendency being toward conservative measures. Recovery may occur after simple laparotomy without resection. If the disease is advanced or very extensive, resection is indicated. One case is reported in detail.

SYDNEY J. HAWLEY, M.D.

Carcinoma of the Large Intestine. Raymond E. Buirge. Arch. Surg. **42:** 801–818, May 1941.

Buirge reviewed the autopsy reports on cases diagnosed as carcinoma of the colon in the Department of Pathology at the University of Minnesota between January 1910 and July 1937. Of 26,798 records 416 were of cases of colonic neoplasm. The sex ratio for this group was 1.86 males to 1 female; for the colonic carcinomas it was 1.77 to 1, or approximately the same. The average age was $50^1/_2$ years. The most common sites were the rectum, sigmoid flexure, and cecum. Rectal carcinoma was about three times as frequent in males as in females. The average duration of symptoms before diagnosis was thirteen months for lesions in the right side of the colon, twelve and a half months for those in the transverse and descending colon, and fourteen months for those of the sigmoid flexure.

The clinical picture was frequently atypical and confusing: 16.6 per cent of the cases incorrectly diagnosed clinically were thought to be appendicitis, and 8.3 per cent were thought to be cholecystitis. A recent hemorrhoidectomy had been done without discovery of carcinoma in 5.2 per cent of the cases of rectal carcinoma. Anemia was a common diagnosis. Symptoms are often vague or absent. Change of intestinal habit was observed in 62 per cent: diarrhea was noted in 57 patients, diarrhea alternating with constipation in 10. Nausea and vomiting were common, but records on this point were incomplete. Painful defecation was observed in 32 instances; change in the character of the stool in 13. Late loss of weight occurred in 85 per cent of cases. Constipation or obstipation were common in cases of obstruction. Obstruction plays a minor rôle in carcinoma of the right half of the colon, 43 per cent of the patients having no evidence of it; while only 13 per cent of the patients with a lesion in the distal colon were free from obstruction of some degree.

Bleeding was a common finding. Hemorrhoids were present in 50 cases. Anemia was consistently observed, being somewhat more pronounced in carcinoma of the proximal colon. Pain was a symptom in only half the cases. The presence of a palpable abdominal mass was variable, depending on the site of the lesion.

Among the diagnostic measures suggested, biopsy and roentgen examination are the most important. The latter was correctly interpreted in 85 per cent, doubtful in 5 per cent, and incorrectly interpreted in 10 per cent of the cases.

Involvement of the colon was circumferential in 30 per cent of cases. Metastases had occurred in 57 per cent, the most common site being the liver.

Two hundred and sixty-five patients were treated by operation, and of these 172 died from some immediate surgical complication. The remainder died of causes other than the intervention.

The author concludes that late diagnosis is unavoidable, owing to poor understanding of the early symptoms; that the clinical pattern of the disease is not specific; that reliable clinical proof of the condition depends on the roentgen ray, with the use of digital examination and the sigmoidoscope in lesions of the distal colon.

LEWIS G. JACOBS, M.D.

Cholecystitis and Cholelithiasis in Children. R. A. Tearnan. Illinois M. J. **79:** 418–421, May 1941.

The author demonstrates clearly that the four "F's"—fair, fat, forty, and five children—must not always be expected in a case of cholecystitis or cholelithiasis. His review of the literature indicates that about 1,000 cases have been reported in children under fifteen years of age. Pain at or near the umbilicus in a child should not be regarded as due to appendicitis too quickly. This, he states, is the most prominent symptom in the majority of cases of gallbladder disease in children. When the surgeon finds a normal appendix he should not fail to investigate the gallbladder. A brief discussion of the etiology and symptoms is given and great emphasis is placed on the consideration of this condition and the importance of x-ray examination and cholecystography in patients giving a history of recurrent spasmodic abdominal pain.

WILLIS A. WARD, M.D.

THE SKELETAL SYSTEM

Malunited and Ununited Fractures of Both Bones of the Forearm. Ralph K. Ghormley. Rocky Mountain M. J. **38:** 358–362, May 1941.

The importance of normal function in the forearm in maintaining normal function of the hand, is, of course, obvious. In all forearm fractures one must have in mind the functional result.

A convenient classification of fractures of both bones of the forearm is the following:

(1) Fractures of shafts, particularly the middle third and lower portions.

(2) Fractures of upper end of the ulna, with dislocation of head of the radius.

(3) Fractures near the wrist, *i.e.*, malunited Colles' fractures.

A most important consideration is the condition of the soft parts. Injuries to nerves, ischemic paralysis, and adherent tendons, all of which so frequently complicate these cases, must be taken into consideration; they may altogether ruin the end-result, even though the fracture alignment be perfect.

Non-union of both bones of the forearm is a severely crippling condition. It is more frequently observed in the lower and middle third of the radius and in the upper third of the ulna. In the author's experience, the massive onlay graft has been the most satisfactory method of procedure. This involves the following steps:

(1) Exposure of the ununited fracture.

(2) Removal of fibrous union by sharp dissection with osteotome or knife.

(3) Preparation of the ends of the bone by freshening with chisel, and cutting them so that they approximately fit each other. In some cases, removal of part of the bone with a saw will be necessary. It may be necessary to drill the ends of the bone where hard eburnated bone is found, in order to open the marrow cavity.

(4) Apposition of the ends of the bone.

(5) Cutting of the surface of fragments of bone until bleeding bone is encountered, for the reception of the graft.

(6) Application of a tibial cortical graft and fixation by means of screws, bands or whatever may be the method of the particular surgeon.

(7) Packing chips of cancellous bone from the tibia about the site of the fracture and along the graft.

In many instances where non-union exists in the presence of a metal band or plate and screws on the fracture, these may be removed at the same time that the operation for bone graft is performed, provided, of course, that there is no infection in the region. When infection exists in the presence of a foreign body, such as a plate or band, the foreign body must be removed and the bone-graft procedure must be postponed until the infection has cleared and the wound remained healed for six months. The same is true when sequestra are present.

An important decision in the treatment of fractures of both bones of the forearm is whether or not to graft bones. It is possible, of course, in many instances to obtain union by grafting one bone and freshening the ends of the second bone, drilling the ends and perhaps packing some chips of cancellous bone about the ends of the second bone to insure healing. In many instances, however, when long-standing pseudarthroses with extensive eburnation of the ends of the bone are present, it is necessary to do a fairly complete operation on each bone in order to insure healing, but it should be borne in mind that in the presence of atrophy and contracture of the soft parts, particularly if much scarring is present, the application of a massive graft on both bones may so increase the bulk of the bony tissue as to make closure of the soft parts difficult.

Plaster fixation after operation must be of sufficient duration to insure union. The minimal time is three months.

A fracture which deserves special mention is that at the upper end of the ulna, with dislocation of the head of the radius. In these cases, some type of transplantation of bone to the ulna is necessary to secure bony union and, in addition, the resection of the head of the radius is often required.

Another type of fracture about which there has been considerable discussion is the malunited Colles' fracture. Ununited Colles' fractures are rarely, if ever, encountered. There are two elements to be considered in the correction of these malunited fractures: first, the dorsal displacement of the distal radial fragment as well as the shortening of the radius; second, the overriding of the distal end of the ulna with impingement on the carpal bones. These may be dealt with in a single or a two-stage procedure. Postoperative fixation must be as prolonged as for bone grafts.

PERCY J. DELANO, M.D.

Nondestructive Tuberculous Polyarthritis versus Tuberculous Rheumatism (Poncet). David H. Kling and Max A. Levine. Arch. Surg. **42:** 956–967, May 1941.

This report deals with a case of the type described by Poncet, a tuberculous polyarthritis resembling in its clinical course the non-specific atrophic type of arthritis.

A woman, aged 34, first consulted the authors in May 1936, with a history of swelling and contracture of the left knee for four years and pains in other joints. There had been repeated close contacts throughout her childhood with members of the family who had open tuberculosis. The patient had suffered from various illnesses, but although tuberculosis was suspected, no positive diagnosis had ever been made. As a child she had experienced vague rheumatic pain in the arms, hands, and feet. At the age of 28 she twisted her left ankle, which became painful, red, and swollen. The left knee also became red and swollen. The roentgen pictures at this time were normal. In 1934 the patient was in an automobile collision and suffered sprains of both ankles; a subsequent thrombophlebitis confined her to bed for several weeks. In the following year she had recurrent transitory attacks of pain in many joints, but the left knee was constantly red and swollen and gradually underwent a flexion contracture. Roentgenograms in 1936 showed a narrowed joint space, slight spurring of the tibia, and roughening of the joint surface laterally.

Treatment by extension, colloidal sulphur injections, streptococcus vaccine, histamine iontophoresis, and colloidal gold injections over a two-year period were of little or no benefit. Baths at the spa at Pistyany, Hungary, provoked severe reactions. A check-up was made at Vienna, and Dr. R. Kienboeck interpreted the roentgenograms as "benign tuberculous rheumatism, Poncet type." There were atrophy of the bones and thinning of the articular cartilages with superficial erosion of the intercondyloid eminences of the tibia; on the left, slight porosis of the head and neck of the femur, and osteophytes over the greater trochanter. The ankles showed slight porosis. Four roentgen treatments were given to the knee and a brace was prescribed.

Symptoms persisted, however, and in April 1938 the sedimentation rate was 60 mm. in one hour. Postpharyngeal infection of mild degree with *Streptococcus viridans* was discovered. An aspiration of the left knee and injection of the fluid into a guinea-pig was without result. No visceral tuberculosis was found. An orthopedist diagnosed the condition of the left knee as tuberculosis. In August 1938 synovectomy and fusion were done, with prompt bony union between the tibia and femur. Paraffin sections showed a few small conglomerate tubercles. Only two bacilli were found in 25 sections, but guinea-pig inoculation now led to the recovery of a pure strain of human tubercle bacillus.

While the patient's knee is painless and only causes a slight limp, the articular pains elsewhere are practically unchanged.

Most of the American consultants considered this a simple rheumatoid arthritis, while the Viennese consultants believed it to be a Poncet type of tuberculous arthritis. Even though they were right, however, the changes observed do not impress the author as characteristic. The diagnosis of monarticular tuberculous arthritis, although partly correct, ignores much of the course and the symptoms in the other joints.

The description of Poncet and his followers has included a medley of acute, subacute, and chronic conditions without distinctive clinical features. Many theories of pathogenesis, including that of causation by "toxins," have been advanced. It is not demonstrated, however, that tubercle bacilli produce exotoxins. Sensitization also seems an unsatisfactory explanation. These factors have hindered the adoption of Poncet's views.

This case proves that such a mild type of tuberculous arthritis may occur. Definite tubercles were demonstrated in the joints. Whether all similar cases are tuberculous is doubtful. In cases of mild polyarthritis suspected of being tuberculous on clinical grounds, a presumptive diagnosis of non-destructive tuberculous polyarthritis may be made.

LEWIS G. JACOBS, M.D.

Acute Trochanteric Bursitis with Calcification. Albert J. Schein and Otto Lehmann. Surgery **9:** 771-779, May 1941.

The analogy between calcific subdeltoid bursitis and calcific trochanteric bursitis has been noted by several of the authorities mentioned in the authors' review of the literature. This article presents the clinical picture of acute trochanteric bursitis with calcification as seen in 7 cases, 3 in males and 4 in females.

The presenting symptoms were remarkably constant: severe pain in the hip region with inability to walk about, coming on less than forty-eight hours before examination. The outstanding physical findings were exquisite localized tenderness over the greater trochanter, severe pain on abduction and rotation of the affected hip, little or no pain on flexion, and no tenderness over the hip joint proper. Five patients had slight temperature elevation.

X-rays showed calcification in all cases, but the density, configuration, and position of the shadows varied. In 5 cases the calcification was situated lateral to the upper part of the greater trochanter; in 2 it was above the tip of the greater trochanter.

The course was acute, lasting three days in six patients. The calcification disappeared after about one month. Any type of treatment which produces hyperemia, such as x-rays, infra-red therapy, or diathermy, is satisfactory. J. E. WHITELEATHER, M.D.

Congenital Changes of the Hip Joint as a Source of Misdiagnosis and Mistreatment in Childhood. Wilhelm Leun. München. med. Wchnschr. **88:** 552-555, May 9, 1941.

Congenital dislocations of the hip may not be seen until the late stages, the child having been considered "rheumatic," and roentgenograms are sometimes subject to misinterpretation because of secondary changes in the femur or acetabulum. Several cases are reported in which a unilateral luxation was variously regarded as a tuberculosis of the hip, Perthes' disease, and nonspecific coxitis, apparently because of cystic rarefactions in the femoral head. Narrowing of the joint space may also be present.

In the congenital lesion it is to be noted that the principal changes are in the top of the joint, at the point of maximum displacement, while the bony contours are sharply marked in contrast to the irregularity and atrophy in coxitis. Decalcification is the rule in inflammation, while in congenital dislocation there is a condensation of calcium in the subchondral zone. The cystic rarefactions in congenital dislocation are sharply bounded, while in specific lesions they fade gradually into their surroundings.

The changes of Perthes' disease are easier to distinguish, especially the characteristic sparing of the acetabulum and the change in the neck of the femur. This latter, however, may be simulated by external rotation, and some broadening in the nature of a coxa vara may occur in the late stages of congenital dislocation. There is little danger of confusing congenital dislocation with a recent trauma. Confusion with coxa vara adolescentium occurs; in the latter condition the slipping down of the epiphysis of the head on the upper side must also be present. The reverse mistake may be made, and a case of tuberculosis of the hip so misdiagnosed is presented.

The cardinal signs of congenital dislocation should always be sought: acetabular flattening, erosion of the socket at the site of greatest weight bearing, double socket formation, mushroomed femoral head, and

widening of the neck. In the late stages cystic changes may occur.

Several roentgenograms are reproduced.

LEWIS G. JACOBS, M.D.

Platybasia. Paul J. Laube and Oscar Turner. Yale J. Biol. & Med. **13:** 644–648, May 1941.

Two cases of platybasia are presented in detail, including the history and clinical findings. One case is of particular interest in that there was considerable relief of symptoms following a suboccipital craniotomy and cervical laminectomy. At operation the posterior arch of the atlas appeared to be completely absent and the second cervical spine was in close approximation to the base of the skull. The arch of the atlas was replaced by a dense band of fibrous tissue. The left cerebellar tonsil was herniated down to the level of the third cervical vertebra and was reduced only after the dura was severed through the band of tissue described above. The cerebellar tonsil was found to have produced a considerable indentation on the underlying medulla just to the left of the calamus scriptorius. The posterior inferior cerebellar artery had been elongated by the displacement of the cerebellar tonsil and appeared quite redundant. While relief of symptoms following the operation was not complete, there was definite improvement.

In the second case the typical x-ray findings at the base of the skull were present. This patient had a spontaneous remission of symptoms without treatment.

The authors feel it is best to restrict the term platybasia to those cases which presumably have a congenital basis for the cervical occipital deformity.

ANDREW H. DOWDY, M.D.

Spondylolisthesis Affecting the Fourth Lumbar Vertebra. W. M. E. Topping. Brit. J. Radiol. **14:** 162–163, May 1941.

Two cases of spondylolisthesis involving the fourth lumbar vertebra are reported. Both occurred in middle-aged laborers. There was no history of trauma.

SYDNEY J. HAWLEY, M.D.

Chloroma. T. A. Kemp and E. Rohan Williams. Brit. J. Radiol. **14:** 157–161, May 1941.

Chloroma is a tumor-like hyperplasia of the leukocytic parent cells affecting chiefly the skull and facial bones and less frequently the sternum, ribs, vertebrae, femora, pelvis, and tibia. The deposits are subperiosteal, medullary, and cortical. The lymph nodes are affected in about half of the cases. The blood count resembles that of acute myelogenous leukemia.

The disease is commonest in male children, five to six years of age. Tumors are present in the skull, particularly the frontal regions. These do not always show the typical greenish hue. The blood changes are not always marked. Death usually occurs within eighteen months. Therapy is usually of no avail.

The radiological features are periosteal new bone formation along the shafts of long bones, irregular areas of medullary and cortical destruction, and pinpoint translucence in the skull. One case is reported.

SYDNEY J. HAWLEY, M.D.

THE GENITO-URINARY TRACT

Air Pyelography. Owsley Grant and Robert Lich, Jr. Ann. Surg. **113:** 865–868, May 1941.

The authors review briefly the history of air pyelography, directing particular attention to the work of von Lichtenberg, Dietten, and Hughes, and stressing the technic of Hughes. Air embolism as a possible fatal complication of the procedure is admitted but this danger is minimized if the proper technic is employed.

The technic is discussed in considerable detail. Air is introduced under a pressure of 30 mm. mercury, a 5F catheter being employed. The position of the catheter in the renal pelvis is of great importance. The method of its correct insertion is given in detail. As soon as pain appears injection of air is stopped regardless of how little has been introduced.

Air pyelography is indicated in calculous disease of the kidney. It is especially useful in the localization of small stones or fragments of large ones where accuracy is essential. It is not to be used routinely but is no more hazardous in selected cases than halogen pyelography; it is less irritating and causes less postoperative reaction.

HORACE C. JONES, M.D.

Differential Diagnosis of the Hematurias with Report of Two Rare Cases. R. Weyeneth. Schweiz. med. Wchnschr. **71:** 501–505, April 12, 1941.

A report is made of two cases of hematuria in which the diagnosis was established only by operation. The first patient was a man of 70, with a severe hematuria which had appeared suddenly about ten years before and been present intermittently since. At first, bleeding was painless but always profuse; the day before entry severe pain on the right side had appeared. Examination showed continuous urethral bleeding with clots. Pain was present on the right, radiating to the groin and bladder. The lower pole of the right kidney was palpable. Cystoscopy showed that the bleeding was from the right ureter. A mild anemia was present, and the blood urea was 50 mg. per cent. A retrograde pyelogram with 4 c.c. of thorotrast showed a normal left kidney, while the right upper ureter was dilated and ended in a crescentic defect. On a diagnosis of tumor, a ureteronephrectomy was done, following which the patient recovered and has remained well. Pathological examination showed 2 papillomas of the ureter, 2 cm. below the renal pelvis. These were rather vascular and in places the basement membrane was absent.

The second case was that of a woman of sixty-five with severe hematuria. After a fall in 1923 she complained of pains on the left side. These recurred with varying severity, and in October 1939 came on very severely. They were always colicky. The patient had lost weight and complained of hematuria. On examination a resistant feeling in the left abdomen, a moderate anemia, and an elevation of the blood urea to 49 mg. per cent were noted. Cystoscopy showed delay in dye excretion on the left (20 min. against 3 min. on the right). Retrograde pyelograms showed a normal picture on the right, but on the left the ureter was sharply kinked at the uretero-pelvic junction, the pelvis was dilated, and the upper calyx deformed; the kidney shadow was enlarged as well. On a diagnosis of neoplasm, in spite of the atypical pyelogram, a nephrectomy was done. A tumor, the size of an orange proved to be a pseudo-cyst filled with blood. This was of the type called perirenal hematoma or Wunderlich's disease. External bleeding was due to a connection with the renal pelvis.

Hemorrhages of the type in this second case may be intrarenal and terminate in repair and fibrosis, or intracapsular, as here. Rupture in such a case may lead to an extracapsular hematoma. Various classifications as to location are of no great clinical importance. Hemorrhage into the adipose capsule or the suprarenal capsule is rare. Three cardinal symptoms are described, (1) sudden severe pain in the renal region; (2) signs of internal hemorrhage (anemia); (3) development of a retroperitoneal hematoma. Symptoms may mimic digestive tract disease, especially mesenteric thrombosis. Vomiting and ileus are common. Distinction from retroperitoneal neoplasm may be made by the rapid growth of the tumor, which often reaches the size of a baby's head in a few hours. Fever may be present with

the painful crises but is not constant. Hematuria is found in only a third of the cases. The disease pursues a rapid course, usually without necessity of intervention. Death may be due to hemorrhage, intestinal obstruction, or pulmonary complications. Differential diagnosis includes hydronephrosis, polycystic kidney, perinephric abscess, gallbladder disease, ileus, acute appendicitis, and tubal abortion. With care the diagnosis should not offer much difficulty, as only two conditions present a very similar clinical picture, namely, "struma suprarenalis cystica hemorrhagica (Henschen)" and renal infarct. Treatment should be surgical, with only a few exceptions. Ablation of the pseudo-cyst should be performed if old changed blood is found; otherwise a simple tamponade suffices. Nephrectomy is only to be done in selected cases. Operation in hemophiliacs is absolutely contraindicated.

LEWIS G. JACOBS, M.D.

THE CENTRAL NERVOUS SYSTEM

Reduction of Pain and Other Undesirable Reactions due to Pneumo-Encephalography. T. J. C. von Storch and H. H. Karr. New England J. Med. **224:** 755–759, May 1, 1941.

Pain, hyperthermia, nausea, vomiting, aseptic meningitis, urinary retention, and shock are the common disagreeable reactions to pneumo-encephalography. Their incidence, however, may be reduced by proper preparation of the patient, consisting in sedation, limitation of fluids and food, and the administration of atropine sulphate (gr. 1/150 to 1/50). Analgesia produced by morphine, scopolamine chloral hydrate, oral nembutal and amytal may be effectively used in a co-operative patient. Frequently anesthesia is necessary. For this the authors prefer pentothal sodium because of the possibility of better control.

Filtered air, room air, carbon dioxide, nitrogen and helium are the gases usually employed in the procedure. Others have been tried experimentally in animals and rarely in man. Room air is most commonly used but oxygen is frequently advocated. An amount of gas sufficient to replace the fluid withdrawn from the spine is introduced. Methods of drainage and gas replacement vary, the important consideration being to disturb the patient as little as possible. This means carrying out the procedure near the x-ray department.

Shock is combatted by coramine, caffeine sodium benzoate, and warmth. Fluid replacement must be encouraged. Codeine and aspirin will usually relieve headaches.

J. B. MCANENY, M.D.

Immediate and Late Effects of Intrathecal Injection of Iodized Oil. A. W. Marcovich, A. Earl Walker, and C. M. Jessico. J. A. M. A. **116:** 2247–2254, May 17, 1941.

In order to assess reactions, the authors have reviewed 150 cases in which iodized oil was used to examine the spinal canal. Usually 2 c.c. of oil were used, but in a few cases 4 c.c. were introduced. In most cases injection was by lumbar puncture.

Immediate Effects: There was no subjective reaction in 46 per cent of the series. Fever of low grade was the most common sequel, lasting twenty-four to forty-eight hours. Twenty-three patients complained of headache. Aggravation of previous symptoms is not an uncommon occurrence. It must be remembered, however, that lumbar puncture alone may be followed by exaggeration of symptoms in cases of tumor of the spinal cord.

In the spinal fluid, at about twenty-four hours after injection, a pleocytosis is noted, with as many as 100 cells per cubic millimeter. Occasionally this may rise to 1,000. The reaction apparently reaches its height on the second, third, and fourth days. The total protein of the spinal fluid also tends to increase after the injection. This persists for several days. Blood-stained fluid suggests a generalized congestion of the spinal vessels. No increase in the spinal fluid pressure has been observed.

The authors have had no fatalities referable to injection of iodized oil. A few deaths have been reported by others. In these cases there were many complicating factors, and the etiologic relationship of the iodized oil to the fatal outcome is difficult to evaluate.

Late Effects: No definite, deleterious, permanent clinical ill effects can be ascribed to introduction of the iodized oil into the subarachnoid space.

In those patients who had had no operation and were later examined roentgenologically, the greater part of the iodized oil was found to be freely movable in the subarachnoid space. In almost all cases a few globules were fixed in the root sheaths of one or more of the nerves of the lower part of the spine. In no instance had the oil been completely absorbed. In 24 cases in which an operation was done, the oil was usually fixed within the tissues and immobile. If the dura mater has been opened the iodized oil is rapidly encysted by the proliferation of the arachnoid membrane. Frequently much of the oil is present in the tissues outside the spinal canal.

As to the effect on the brain, those patients who had encysted intracranial iodized oil had no symptoms referable to its presence.

Three case histories are given, with pathologic findings in the cord following injection of oil some time before death. In two of these cases no operation had been done and in a third a laminectomy was performed and the dura opened. In all three cases fine adhesions were present between the dura mater and the arachnoid membrane. Other factors, however, could have been responsible for these changes. Constant pathologic changes in the human spinal cord following the injection of iodized oil are minimal. This is in contrast to the changes noted in the cord and membranes of animals, where the changes are fairly severe. Constant parenchymal changes are not present in man.

The slight pathologic changes in the spinal cord and its coverings agree well with the fact that the iodized oil in patients not operated on is usually movable and flows freely up the cord to the basal cisterns. If severe arachnoiditis were present one would expect the iodized oil to produce numerous partial or complete obstructions within the spinal canal.

Injected iodized oil slowly becomes fixed in the sheaths of the spinal nerves and the caudal sac if the dura is not opened. Pia-arachnoid reactions are more likely to occur when the dura has been opened.

CLARENCE E. WEAVER, M.D.

FOREIGN BODIES

Foreign Bodies in Air and Food Passages. A. Greifenstein. München. med. Wchnschr. **88:** 599–605, May 23, 1941.

The author refers to an article of H. Schäfer (München. med. Wchnschr. **87:** 1112, 1940), which he believes contains errors commonly made in the diagnosis of foreign bodies. The usual story is that something held in the mouth is inadvertently swallowed because of drinking, laughing, sudden fright, or because of its own slipperiness; or that something has slipped down during hurried eating, especially in children. As a matter of fact 40 per cent of foreign bodies in children are bronchial and only 10–20 per cent esophageal. Because of its size or the presence of points the foreign body may lodge in the lower pharynx. It is helpful if the patient brings a duplicate of the suspected foreign

body, as this aids in the roentgen localization. In each case three points must be settled: (1) Is the foreign body lodged in the air passages, or (2) is it in the esophagus? (3) If it has entered the esophagus, has it progressed to the stomach?

Lodgment in the air passages is seldom missed. Cough is an outstanding symptom, and is usually of a spasmodic character. Varying degrees of dyspnea occur in the intervals.

In the esophagus the foreign body lodges in one of the physiological narrowings; about 70 per cent lie in the upper third. Subjective sensation is a poor localizing sign. In the cases in which non-blocking foreign bodies have passed into the stomach it is necessary to prove by roentgenoscopy, or even by esophagoscopy, that one or more do not remain in the esophagus. The presence of an organic stenosis may lead to the lodgment of a foreign body; this is sometimes the first evidence of a carcinoma.

The most important aids in diagnosis are mirror examination of the larynx, roentgenography, and direct speculum inspection (tracheobronchoscopy and esophagoscopy). While roentgenoscopic and roentgenographic diagnosis seems simple, errors are no rarity. Pitfalls to be particularly avoided are misinterpretation of calcified lymph nodes, calcified goiters, calcified tracheal cartilages and costal cartilages; failure to recognize non-opaque or poorly opaque foreign bodies; mistaking upper esophageal foreign bodies for tracheal ones or bodies at the tracheal bifurcation for esophageal bodies. Filling the esophagus with contrast media is generally of little help and unnecessary, since it cannot replace esophagoscopy. Before endoscopy or operation one should always make sure that the position of the foreign body has not changed; reliance should not be placed on the roentgenogram the patient brings with him.

One sometimes sees a patient with a "chronic" esophageal foreign body. This is often symptomless; pain as a rule indicates injury to the wall and inflammatory swelling.

Chronic bronchial foreign bodies are no rarity. This is particularly true of bodies not roentgenologically demonstrable. A short dry cough, fever, and bronchial and pulmonary complications are characteristic; the condition is frequently confused with other pulmonary diseases. Some physicians incorrectly believe that these may be left untreated; but inflammatory changes in the distal bronchial tree always ensue.

Both acute and chronic bronchial foreign bodies may lead to roentgenological changes in the lung. Acute obstruction leads to atelectasis with clouding of the lung and displacement of the mediastinum to the diseased side. A partial obstruction may lead to an emphysema of the affected side with wandering of the mediastinum to the unaffected side in expiration. For this reason fluoroscopy is a better localizing method than roentgenography.

The most certain diagnostic measure is endoscopic exploration. It has the special advantage that the foreign body can be removed as soon as found. The method is painful in only a minor degree and in the last ten years the author has had no fatality or serious complication, although he performs 300 to 400 endoscopies per year. Even in very sick patients it is more important to remove the foreign body than to avoid the strain of this examination.

LEWIS G. JACOBS, M.D.

Localization and Removal of Foreign Bodies in War Injuries. A. Zuppinger. Schweiz. med. Wchnschr. **71:** 716–719, June 7, 1941.

The author discusses the subject of foreign body localization in general, and then describes an ingenious roentgenologic localizing method as follows:

With the foreign body centered under the screen its projection is marked on the flesh. The shutters are then opened to a width half the focus-screen distance. The tube is shifted laterally until the shadow of the foreign body strikes the exact edge of the field, and a mark is placed here. The tube is next shifted until the shadow touches the other edge of the field, and a mark again made. A piece of cellophane previously mounted over the glass of the screen allows this to be a permanent record. The distance between the two marks of the foreign body shadow multiplied by two is equal to the depth of the foreign body beneath the center of the screen. Since the height of the screen above the skin is readily measured, the depth beneath the mark on the skin is at once known. A geometrical proof of the correctness of this method is given, with some suggestions about apparatus for field use.

LEWIS G. JACOBS, M.D.

A New Apparatus for Localizing Metallic Foreign Bodies. Hans Oberdalhoff. München. med. Wchnschr. **88:** 353–354, March 28, 1941.

Two new foreign body localizers have recently appeared on the market. One, the Boloscope, manufactured by the Phillips factory in Holland (Eindhoven), employs biplane fluoroscopy with two thin pencils of x-ray crossing at the level of the foreign body. Subsequent reconstructions in daylight give a precise localization. This apparatus has certain inherent limitations; it can localize only bodies large enough to be seen on the screen, and in the cases of the lighter metals this size may be considerable; it also requires the availability of trained radiological personnel; the position in which one can work on the patients is limited, which may interfere with surgical approach.

The Siemens-Reiniger factory in Berlin is now producing a "Metallsucher" (metal-seeker) for metal localization. This consists of two high-frequency transmitters, one with fixed frequency and a second with its transmitting loop built into a glass sound with an exploring tip, this one being fitted with a variable condenser so that the two high-frequency fields may be opposed to each other. When the fields are together, a tone in a loud-speaker is audible. If the tip approaches a metal body, it changes the inductance of the exploring loop, and thus the difference between the two fields, which alters the tone in the loud-speaker. This may vary from the deepest bass to the highest treble. Through interference the tone may be caused to disappear in the same manner. Since electromagnetic waves penetrate the body, the position of the patient is immaterial, and the smallest foreign body may be detected. The magnetically permeable metals, nickel and iron, show a reversal of the direction of the tone change from other metals. The apparatus is furnished with two tips, one 18 mm. in diameter, which will detect a foreign body within 6 cm., and one 10 mm. in diameter, which will detect a foreign body within 3 to 4 cm. It is of course necessary to cut down to within this distance of the foreign body, and to have all metallic instruments more than 10 cm. from the field; also wires and clips cannot be present in the wound.

In the last four months 75 foreign bodies from 65 patients have been successfully extracted with this apparatus, some of them the tiniest splinters, invisible by x-ray. In some cases the wound led in one direction and the sound in another, but the sound was always right. This device seems more practical in the field than x-ray apparatus. LEWIS G. JACOBS, M.D.

AIR RAID CASUALTIES

X-Ray Examination in Relation to the Treatment of Air Raid Casualties. Maj. E. Samuel. Brit. J. Radiol. **14:** 171–174, May 1941.

Air raid casualties, from the radiological standpoint, may be classified as (*a*) penetrating wounds, due to

glass, metal, masonry and bomb fragments, (*b*) crushing injuries, and (*c*) combined injuries.

Most of the glass injuries are due to plate glass, which is usually dense enough to be demonstrated. Penetration about half way between that for bone detail and soft tissue detail is best. Glass fragments almost never produce fractures. Most of the fragments, of whatever material, are discovered and removed during the surgical toilet of the wound. Some are spontaneously discharged. Localization is not advisable until the patient has recovered from shock. Film methods of localization are more suitable for this work than fluoroscopic localization. Gas gangrene may be discovered early by x-ray. Serial examinations should be used, to avoid error in interpretation due to gas sucked in by muscle action, or driven in at the time of the accident. Scalp injuries, except those due to flying glass, should be rayed early to discover depressed and *contracoup* fractures.

Basal bronchopneumonia is common in crushing injuries of the chest, probably due to the combination of shock, exposure, and anesthesia.

SYDNEY J. HAWLEY, M.D.

TECHNIC

A Research into the Physical Factors Concerned in Indirect Radiography. Paper II. Light Transmission of X-Ray Protective Lead Glass. R. Herz and B. Stanford. Brit. J. Radiol. **14:** 181, May 1941.

X-ray protective lead glass impedes the light from the fluorescent screen about 12 per cent in the blue-green and yellow-green region. As it is doubtful if a difference of 20 per cent in illumination is detectable on the film in practice, the interposition of lead glass between the screen and the lens in mass radiography will not interfere. SYDNEY J. HAWLEY, M.D.

RADIOTHERAPY

MALIGNANT NEOPLASMS

Carcinomas of the Breast and Their Treatment: A Critical Review. Paul Desaive. Rev. belge d. sc. méd. **13:** 151–175, April, and 209–238, May 1941.

The author begins by reviewing the embryology, anatomy, and histology of the breast. In concluding this section of his article he calls attention to a sternal and to an axillary prolongation of the gland which may be present, and to the occurrence of malignant growth in such aberrant tissue.

Most tumors of the breast begin with a rather discrete nodule, though not all may be observed at this stage. In Desaive's material, there is a slight predominance of left-sided lesions (52 per cent). He also finds some constancy as to breast quadrant, 56 per cent of the cases involving the upper and outer quadrant of the breast.

He stresses the fact that the tumors are hard; and this hardness is found even in the cystic forms. Extension then takes place along the following channels:

(*a*) Outward, toward the cutaneous surface, resulting in
- (1) Fixation or retraction of the nipple
- (2) Cutaneous tufting
- (3) Development of the *peau d'orange* (orange skin) by enlargement of the secretory orifices by edema, due to compression of the lymphatics, and by direct infiltration of the skin proper
- (4) The occurrence of vesiculation and ulceration in the infiltrated tissues.

(*b*) Inward, producing:
- (1) Immobilization of the gland along the thoracic side
- (2) Involvement by lymphatic edema of parts not yet involved by carcinomatous extension.

Most often extension occurs in two directions, (outward and inward) simultaneously. If the tumor takes origin in the large ducts under the nipple, the first symptom may be a blood-stained discharge—the so-called *blutende Mamma* of the German writers. If there occurs a preliminary dilatation of the duct, the lesion may take on for a time a cystic aspect, though the "pericystic" induration should prevent one mistaking the true nature of the process.

If the principal pathologic process is cutaneous, one finds the Paget form of the disease; if the primary lesion is found in one of the above-mentioned prolongations of mammary tissue, then an "extra-mammary" cancer is produced.

The variations in type are mentioned—encephaloid, scirrhous, medullary, pustular, erysipeloid, and finally, a form encountered often in young women, one in which the common symptoms of inflammation appear to predominate, the *mastite néoplasique* of Volkmann, which is usually rapidly fatal.

The author comments, with some discouragement, upon the polymorphism of the present classifications, making the point that an infinity of terms prevents one getting hold of a workable and useful classification and hence leads to endless and harmful confusion.

The significance of extension to the lymph nodes is summarized by an appraisal of its relation to five-year cures:

No adenopathy......61.6% five-year cures.
Small, mobile, axillary nodes....43.7% five-year cures.
Large, fixed, axillary nodes....22.5% five-year cures.
Subclavicular nodes or axillary nodes on the opposite side....no five-year cures.

Though the duration of the disease (unattended medically) varies from a few months to many years, the average untreated case was found by Hoffman to run a course of approximately 27.7 months. The passage of the past fifty-five years has not altered conditions in this respect. In 1885, when Winiwarter tabulated cases which were "unsuccessfully" operated upon and which had no operation at all, the average duration of life for the operative cases was given as 37–40 months; for those not operated upon, 27–30 months.

Local recurrences may take place eight, ten, or even thirteen years after operation; visceral recurrences at such late dates are less frequent. Nevertheless, one authenticated case appears in the records in which mesenteric metastases appeared twenty-three years after the removal of a breast for carcinoma.

Quoting Cryssel and Morel, and Leddy and Desjardins, the author gives the incidence of recurrences as follows:

Local	38%
Lymphatic	15–20% (C. & M.); 47% (L. & D.)
Osseous	27–33%
Pleuro-pulmonary	12–19%
Opposite breast	2.5%

Differential diagnosis must take into consideration chronic cystic mastitis, benign tumors, the chronic

infectious granulomata such as actinomycosis, echinococcus disease, and tertiary syphilis. Tuberculosis is probably encountered more frequently than is commonly believed. A clue to the latter condition may often be found in inordinately enlarged lymph nodes.

Desaive is not enthusiastic about needle biopsy; he prefers the removal of a piece of tissue by the electrocautery knife. He is not of the opinion that operation must follow immediately upon the biopsy; no one knows just how long is required for lymphatic extension of cells possibly liberated by the cautery knife. He quotes Adair, who found the end-results in the treatment of breast cancer not jeopardized by the practice of biopsy.

In prognosis, one may anticipate the best results between the ages of fifty and sixty; the duration of the disease before operation is of course important, Guénin (see J. de chir. **54:** 332, 1939) finding the following relationship:

Duration 1 month	69%	5-year cures
Duration 12 months	35.6%	5-year cures
Duration more than 12 months	24%	5-year cures

The prognosis is of course less favorable in women below the age of menopause. It is worse when the tumor lies in the supero-internal portion of the breast, since the internal mammary lymphatics and the lymphatics of the opposite side are more readily involved. Histologically, invasion of the blood vessels is of some prognostic significance.

The age incidence in 297 cases of mammary cancer seen in the Liége anti-cancer center was as follows:

20–29	4 cases
30–39	22 cases
40–49	66 cases
50–59	98 cases
60–69	77 cases
70–79	27 cases
80–89	2 cases
90–99	1 case

There were 4 males in the series (1.3 per cent).

Carcinoma of the breast appears to be least common among the Japanese, although they frequently have malignant tumors of the genital organs.

Experimental work on mice, by various investigators, is reviewed, to show the effect of ovarian activity on the rate of growth of carcinoma.

The influence of heredity, trauma, social conditions, and mammary function are commented upon by the author to close the preliminary discussion; none of these factors except heredity is regarded as very vital. Chronic cystic mastitis is stressed as being a significant lesion, and the arguments of those who have attributed to it precancerous characteristics are presented.

Part II of this exhaustive review is concerned with problems of treatment. As a first division, the author takes up surgery.

Credit is given to Halsted for his work in introducing to the profession the cardinal principles of the surgical treatment of breast carcinoma. The modifications of his original operation are listed. To summarize, the following steps are usually considered necessary: adequate skin incision; finding of accurate lines of cleavage; resection *en bloc* of the breast, the pectoralis major, the pectoral fascia; ablation of the pectoralis minor and cleaning out of the axilla, followed by the cutting away of the entire mass and hemostasis and other procedures incident to closing.

Under the heading *Radiologic Technics* the history of radiotherapy in carcinoma of the breast is reviewed, the progress made as equipment permitted of greater penetration being carefully described. Supervoltage therapy is not considered superior, at the present time to that obtainable at 200 kv. The technic of Wintz calls for 200 kv., 2–4 ma., 1 mm. Cu with 2 mm. Al, 70 cm. distance, rays at right angle to field. Three large fields are employed (400 to 700 sq. cm.), anterior, posterior, and supraclavicular, with 90–104 per cent of a skin erythema dose to a field, or about 2,400 r. Treatments are divided, being given at twelve to eighteen-hour intervals, the whole to be administered in eight to fifteen days. This course of treatment is repeated in two or three months.

Other methods of treatment are described: that of Holfelder, in which the factors employed are similar to those in the Wintz method, but in which only half a skin erythema is attempted per field, the plan being to achieve a "saturation" similar to that of Pfahler; the technics of Coutard and Belot, in which fractionation and protraction are applied to the treatment of breast lesions as Coutard first applied them in the larynx; the methods of Richard and Chaoul in dealing with superficial recurrences by means of low voltage.

The application of radium in many forms is discussed in full detail, from the use of the radium bomb consisting of as much as 12 grams, to various means of dealing with local recurrences by plaques and needles.

To summarize, the author enunciates ten principles, which he refers to as his "ten commandments" and which govern his method of dealing with a breast carcinoma from diagnosis to postoperative management. The gist of these tenets may be given as follows:

First Principle: Biopsy is indispensable.

Second Principle: Radiation therapy should never be relied upon, in itself, to cure a carcinoma of the breast.

Third Principle: When axillary adenopathy exists, the axilla should be cleaned out.

Fourth Principle: The affected breast should be removed *in toto*, along with any involved lymph nodes.

Fifth Principle: Every carcinoma of the breast operated upon should receive postoperative irradiation. Each field should receive from 1,800 to 3,000 r, and treatment should be started as soon as the cicatrix is firm.

Sixth Principle: Preoperative irradiation is permissible if it does not delay operation more than five weeks.

Seventh Principle: A supraclavicular node should be removed.

Eighth Principle: In the presence of a postoperative local recurrence the author prefers radium puncture; in an ulcerated lesion, the radioknife (*bistouri électrique*); with multiple nodules, either radium plaques or low-voltage radiation.

Ninth Principle: Roentgen therapy is recommended for osseous metastases.

Tenth Principle: In the so-called inoperable cases, a combination of palliative measures may do much to alleviate suffering. PERCY J. DELANO, M.D.

Relation of Solar Radiation to Cancer Mortality in North America. Frank L. Apperly. Cancer Research **1:** 191–195, March 1941.

Discrepancies in the claims of different authors regarding the relationship of the incidence of skin cancer to general cancer can be explained on the basis of climatic variations. This relationship is inverse in warm climates, direct in colder, less sunny areas. Available statistical records of the farming population of some American states and Canadian provinces show that solar radiation exerts two effects: in districts with a mean temperature of less than 42° F. increasing exposure produces a fall in total mortality from cancer and in the incidence of skin cancer; above 42° F. skin cancer rises despite the relative increase in general immunity to neoplastic disease. Ultra-violet light, therefore, and not actual skin cancer may favor the development of this immunity. Suitable exposure of the skin is suggested as a method of reducing the incidence of malignant growth. The paper is accompanied by illustrative graphs. MILTON J. EISEN, M.D.

NON-MALIGNANT CONDITIONS

Roentgen Therapy for Rheumatic Disease. C. J. Smyth, R. H. Freyberg, and W. S. Peck. J. A. M. A. **116:** 995–1001, May 3, 1941.

Most of the patients selected for this study had comparable rheumatic involvement in pairs of joints. In these patients, one of the pair of joints involved was treated with roentgen radiation and one was left untreated to serve as a control. The technic was the same on all patients: 200 kv. (175 kv. constant potential equivalent); 0.5 mm. copper and 1 mm. of aluminum filtration; 50 cm. skin-target distance; minute output of 50 roentgens (measured in air); usual size of field approximately 15 × 15 cm. Each field was treated three times, receiving 200 roentgens at each sitting. Treatments were given every other day, the total dose being 600 r. Most of the patients received three such series of treatments to the same parts, with intervals of four to six weeks.

Of 57 patients with rheumatoid arthritis 44 per cent received no benefit from roentgen treatment, and in 74 per cent there was no objective evidence of improvement. Of the 26 per cent in whom objective evidence of benefit occurred it was of significant grade in only 14 per cent. In 21 per cent of the group the subjective improvement, which was the only benefit noted, lasted for less than one month. Fifteen additional patients were studied for subjective benefit of psychogenic origin by using a lead screen to prevent roentgen rays from reaching the part to be treated. In all but three of these as much benefit occurred when the parts were screened as when they were actually irradiated. Thus it is shown that much, but not necessarily all, of the subjective benefit may be of psychogenic origin. No evidence that the therapy given protected joints from exacerbations of acute inflammation was found.

Fifteen cases of spondylitis rhizomélique were treated, and 74 per cent were definitely benefited, 67 per cent to a significant degree. No great improvement of motion was, of course, to be expected in those patients with extensive calcification of ligaments.

Twelve patients with non-articular rheumatism and degenerative disease of the joints (hypertrophic arthritis) were treated. The results in general were discouraging. Part at least of the symptomatic benefit was psychogenic.

Definite decreases in the rate of sedimentation of erythrocytes occurred in only 15 per cent of the patients with rheumatoid arthritis. There was a decrease in rate in 40 per cent of those with spondylitis rhizomélique.

No anatomic improvement was demonstrated roentgenologically in any case.

Study of 12 patients with rheumatoid arthritis showed a decrease in the cell count of the synovial fluid in 3. There was no correlation between cell content and clinical effects of roentgen therapy.

In 5 cases of rheumatoid arthritis capsular tissue was studied histologically. No change due to roentgen therapy was recognized.

Twelve per cent of those with rheumatoid arthritis complained of a temporary increase in pain. This did not indicate the subsequent course. Gastro-intestinal symptoms were common in patients treated for spondylitis. These subsided in two or three days after therapy. Of the total group 68 per cent showed no ill effects of any kind.

None of the studies made revealed any information to elucidate the mechanism of roentgen effect in these arthritic cases. The authors do not believe that results depend a great deal on small changes in physical factors of irradiation. Their technic is essentially that of Kahlmeter, whose experience has been the largest and whose results have been among the best reported.

Subjective benefit was reported much more frequently than objective evidence of improvement could be demonstrated. Objectively, decrease in swelling and tenderness and increase in range of motion were observed in the order named. Because of the often encountered natural remissions in chronic rheumatic disease, especially in rheumatoid arthritis, the necessity for careful control of all studies aimed to evaluate any therapeutic procedure cannot be overemphasized. The psychic effect of roentgen therapy can be great. The authors feel, however, that the results in spondylitis suggest that in the majority of cases the benefit is truly a roentgen effect. They recognize that diagnosis of early spondylitis rhizomélique may be shrouded in doubt, but cite 2 cases in which dramatic benefit followed roentgen therapy.

The most important theoretical or practical criticism of roentgen therapy of rheumatoid arthritis is that it is local treatment for a constitutional disease. Patients, however, are often kept incapacitated by one or two joints in particular. Good results were hoped for in this group, but it was here especially that results were undependable and in general discouraging.

CLARENCE E. WEAVER, M.D.

TECHNIC AND DOSAGE

Near-Distance Therapy. Ff. Roberts. Brit. J. Radiol. **14:** 175–176, May 1941.

Near-distance therapy became popular in Germany for the treatment of superficial lesions because of shortage of radium. In evaluating the worth of this type of therapy, it should be borne in mind that the difference between the 50 and 60 kv. used and the 90 and 100 kv. ordinarily employed for superficial therapy is not great. The depth dose at 4 cm. is only 15 per cent less with 60 kv. at 5 cm. distance than with 110 kv. at 30 cm. distance. The distribution of the surface dose with near-distance methods is not as even as with greater distances. Most of the value attributed to near-distance therapy has been shown in rodent ulcer, which is easy to cure by many methods. With modern shock-proof equipment, practically the same result may be obtained with the customary apparatus, so that special equipment is not necessary. The special tube used in contact therapy may have some advantage in intracavitary work, as in the cervix, but the irregularity of the surface dose is a disadvantage. Practically the same result may be obtained with shock-proof apparatus and suitably constructed cones.

SYDNEY J. HAWLEY, M.D.

Accurate Placement of Radon Seed by Suture Method. Fred Hames. South. M. J. **34:** 462–464, May 1941.

An improved method of implanting radon seeds more easily, accurately, and firmly is described. Gold radon seeds are placed in a woven silk suture especially designed so that the seeds are held in place 1 cm. apart. In addition to maintaining the radon in position, the method reduces secondary radiation and is of less discomfort to the patient than other present-day methods of interstitial irradiation.

The radon is placed in position as simply as placing a suture and as simply removed. It is fixed at each end by crushing a hollow lead shot on the suture. A needle screwed into a metal collar at one end of the suture avoids the trauma of passing a double thickness of the suture through the tissue.

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